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### Description

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Phenothiazine derivatives and analogs thereof are useful as inhibitors of the biosynthesis of mammalian leukotrienes. As such, these compounds are useful therapeutic agents for treating allergic conditions, asthma, cardiovascular disorders, inflammation and certain skin diseases.

The leukotrienes are a novel group of biologically active substances derived from arachidonic acid through the action of the 5-lipoxygenase enzyme system. There are two groups of leukotrienes derived from a common unstable precursor Leukotriene A<sub>4</sub>. The first of these are the peptido-lipid leukotrienes, the most important being Leukotrienes C<sub>4</sub> and D<sub>4</sub>. These compounds collectively account for the biologically active material known as the slow reacting substance of anaphylaxis.

The leukotrienes are potent smooth muscle contracting agents, particularly on respiratory smooth muscle but also on other tissues (e.g., gall bladder). In addition, they promote mucous production, modulate vascular permeability changes and are potent inflammatory agents in human skin. The most important compound in the second group of leukotrienes is Leukotriene B<sub>4</sub>, a dihydroxy fatty acid. This compound is a potent chemotactic agent for neutrophils and eosinophils. It also effects other cell types such as lymphocytes and for example may modulate the action of T-suppressor cells and natural killer cells. When injected in vivo, in addition to promoting the accumulation of leukocytes, Leukotriene B<sub>4</sub> is also a potent hyperalgesic agent and can modulate vascular permeability changes through a neutrophil dependent mechanism. See: D. M. Bailey and F. B. Casey, Ann. Rpts. Med. Chem. 17, 203 (1982).

As indicated above, the leukotrienes have been implicated in numerous disease states. Inhibition of leukotriene biosynthesis and/or antagonism of leukotriene action, will therefore provide a therapeutic benefit to patients suffering from leukotriene mediated disease states. These disease states include, but are not limited to; asthma; allergic conditions such as allergic rhinitis; skin diseases including psoriasis and atopic dermatitis; inflammation; gouty arthritis; gall bladder spasms; and cardiovascular disorders such as angina.

Phenothiazine derivatives of the general Formula II are known compounds:

19 296 (1976) and H. B. Collier, Can. J. Med. Sci. 31 195 (1953).

See for example; "Progress in Drug Research", Volume 5, E. Tucker, ed., Birkhauser Verlag, Basel Switzerland (1963) pages 274-383; V. A. Rigas et al., Prostaglandins Med. 183 (1981); J. M. Perel et al., Neurotoxicology, Raven Press, New York, 1977, pp. 9-13; V. Fishman et al., J. Pharm. Exp. Ther. 150 165 (1965); Arch. Intern. Pharm. Ther. 74 314 (1947); N. Bhargava et al., Gazz. Chim. Ital. 109 201 (1979); V. F. Garry et al., Biochem. Pharm. 21 2801 (1972); S. C. Mitchell et al., Drug Met. Disp. 7 399 (1979); T. Akera et al., Biochem. Pharm. 27 995 (1978); I. Creese et al., Europ. J. Pharm., 47 291 (1978); S. C. Mitchell, Drug Met. Rev., 13 319 (1982); T. Ellison et al., Am. J. Vet. Res. (7) 519 (1957); K. P. Singh et al., Asian Med. J.

Several derivatives of phenothiazine are known to be inhibitors of enzymes, including the 15-lipoxygenase enzyme isolated from soybeans. However, none of the compounds of Formula A are taught to have leukotriene biosynthesis inhibiting ability via the inhibition of the mammalian 5-lipoxygenase enzyme system.

It has been discovered that compounds of the Formula II type and analogs thereof are effective inhibitors of mammalian leukotriene biosynthesis and are thus useful in the treatment of conditions such as asthma, allergies, inflammation, psoriasis, and the like in mammals, especially in humans.

Compounds of the Formula II type and analogues thereof may also be used to treat or prevent mammalian (especially human) disease states such as erosive gastritis; erosive oesophagitis; inflammatory bowel disease; ethanol-induced haemorrhagic erosions; hepatic ischemia; noxious-agent-induced damage or necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatoxic agents such as CCl<sub>4</sub> and D-galactosamine; ischemic renal failure; disease-induced hepatic damage; bile-salt-induced pancreatic or gastric damage; trauma- or stress-induced cell damage; and glycerol-induced

renal failure.

The present invention provides pharmaceutical compositions containing a compound of the general Formula I or a pharmaceutically acceptable salt of such a compound, together with a pharmaceutically acceptable carrier, where Formula I is:

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in which

X is Se,S,SO,SO<sub>2</sub> or O;

R¹ is H;  $C_{1-6}$  alkyl; acetyl;  $(C_{1-6}$  acyloxy)- $(C_{1-6}$  alkyl); benzoyl; substituted benzoyl having  $C_{1-3}$  alkyl, halogen, CN, CF<sub>3</sub>, COOR<sup>5</sup>, CH<sub>2</sub>COOR<sup>6</sup>, (CH<sub>2</sub>)<sub>n</sub>NR<sup>8</sup>R<sup>3</sup> (where n is 0, 1 or 2),  $C_{1-3}$  alkoxy, and/or OH substitution, (herein called "substituted as herein defined"); carbamoyl; CO-NHR<sup>7</sup>; COOR<sup>7</sup>; p-toluenesulfonyl; methanesulfonyl; an acyl group such that R¹-OH is an essential amino acid; benzyl; phenethyl;  $(CH_2)$ - $_pOR^a$  where R<sup>a</sup> is  $C_{1-6}$  alkyl or phenyl and p is an integer from 1 to 5 when R<sup>a</sup> is phenyl and is an integer from 1 to 6 when R<sup>a</sup> is alkyl;  $(CH_2)$ - $_pCOOR^6$  where n is 0, 1 or 2; or  $(C_{1-6}$  acyloxy)- $(C_{1-6}$  alkoxy) carbonyl; each of R², R³, R⁴ and R⁵, independently of the others, is hydrogen;  $C_{1-6}$  alkyl;  $C_{2-6}$  alkenyl or - $(CH_2)$ <sub>q</sub>M where q is 0 or an integer from 1 to 6 and M is (a) - $OR^{16}$ ; (b) halogen; (c) - $CF_3$ ; (d) - $SR^{16}$ ; (e) phenyl or substituted phenyl as herein defined; (f)  $COOR^6$ ; (g) - $CO-R^{14}$ ; (h) tetrazolyl; (i) -NH-CO-R<sup>7</sup>; (j) -NR<sup>8</sup>R<sup>9</sup>; (k) -NHSO<sub>2</sub>R<sup>10</sup> where R<sup>10</sup> is OH,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy or phenyl; (l) - $CO-CH_2OH$ ; (m) - $SOR^{11}$  where R<sup>11</sup> is  $C_{1-6}$  alkyl, phenyl, substituted phenyl as herein defined,  $(CH_2)$ <sub>m</sub>COOR<sup>6</sup> where m is an integer from 1 to 6, CN, formyl, or  $C_{1-4}$  perfluoroalkyl; (n) - $CONR^8$ R<sup>9</sup>; (o) - $SO_2NR^8$ R<sup>9</sup>; (p) - $SO_2R^{13}$  where R<sup>13</sup> is hydrogen, OH,  $C_{1-6}$  alkyl, phenyl, substituted phenyl as herein defined,  $(CH_2)$ <sub>m</sub>COOR<sup>6</sup> where m is as defined above, CN, formyl, or  $C_{1-4}$  perfluoroalkyl; (q) - $NO_2$ ; (r) - $O-CO-R^{14}$ ; (s) O- $CO-NR^8$ R<sup>9</sup>; or (t) -CN; each R<sup>5</sup>, independently of the others, is hydrogen,  $C_{1-6}$  alkyl or phenyl;

each  $R^7$ , independently of the others, is  $C_{1-6}$  alkyl, benzyl, phenyl or  $(C_{1-6}$  acyloxy)- $(C_{1-6}$  alkyl); each  $R^8$  and each  $R^9$ , independently of any others, is hydrogen,  $C_{1-4}$  acyl, phenyl, or substituted phenyl as herein defined; or an  $R^8$  and an  $R^9$  are joined through the N to which they are both attached to form a heterocycloalkyl group having from 5 to 8 ring atoms;

each  $R^{14}$ , independently of the others, is hydrogen, (CH), COOR<sup>6</sup> where r is 0 or an integer from 1 to 4;  $C_{1-6}$  alkoxy;  $(C_{1-6}$  alkoxy;  $(C_{1-6}$  alkoxy),  $(C_{1-6}$  alkoxy); phenyl; substituted phenyl as herein defined; or  $C_{1-6}$  aminoalkyl such that  $R^{14}$  COOH is an essential amino acid;

each  $R^{16}$ , independently of any others, is hydrogen,  $(C_{1-5}$  alkoxy)- $(C_{1-5}$  alkyl),  $C_{1-6}$  alkyl; benzyl;  $(C_{1-6}$  acyloxy)- $(C_{1-6}$  alkyl); phenyl; substituted phenyl as herein defined;  ${}^{\bullet}CH_2)_mCOOR^6$  where m is as defined above; CN; formyl; perfluoroalkyl; or  $CH_2-R^{12}$  where  $R^{12}$  is  $C_{1-6}$  alkyl, dimethylamino or phenyl;

and T is hydrogen or  $-OR_{15}$ , where  $R_{15}$  is hydrogen,  $C_{1-5}$  alkyl,  $(C_{1-5}$  alkyl)-acyl, phenylacyl, substituted phenyl-acyl as herein defined; benzoyl; substituted benzoyl as herein defined; or arylsulfonyl; and compounds that are pharmaceutically acceptable salts thereof.

Certain compounds of Formula I and their pharmaceutically acceptable salts are novel.

The numbers surrounding Formula I designate the substituent positions, and R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and T may be positioned anywhere in the structure except at position 10.

The term alkyl, unless otherwise indicated, includes straight chain, branched chain and cycloalkyl groups of the number of carbon atoms shown. The term halogen, unless other indicated, include Cl, Br, I and F.

The  $C_{1-6}$  groups, such as  $C_{1-6}$  alkyl and  $C_{1-6}$  alkoxy, preferably contain 1 to 4 carbon atoms. The term phenylacyl means a group having the formula

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The term aryl includes cyclic structures having the requisite degree of unsaturation to show a characteristic "aromatic" downfiled proton NMR spectrum. Examples include phenyl, substituted phenyl (as defined above in the definiation of R<sup>16</sup>) naphthyl and anthracenyl, and include heteroaryl residues containing one or more O, N or S heteroatoms.

The term essential amino acid includes lysine, tryptophan, histidine, phenylalanine, leucine, isoleucine, threonine, methionine, valine, arginine, alanine, proline, glycine, serine, cysteine, tyrosine, asparagine, glutamine, aspartic acid and glutamic acid.

In those instances when asymetric centres are present, more than one stereoisomer is possible, and all possible isomeric forms are deemed to be included within the planar structural representations shown. Optically active (R) and (S) isomers may be resolved using conventional techniques.

In preferred compositions, X in Formula I is S, SO, SO<sub>2</sub> or O and the other variables are as described above.

In particularly preferred compounds in this group, R2, R3, R4 and R5 are all other than C2-6 alkenyl.

In a first especially preferred embodiment of the invention, the composition contains a compound of Formula I in which X is S or O;

 $R^1$  is H;  $C_{1-6}$  alkyl;  $C_{1-6}$  acyl;  $(C_{1-6}$  acyloxy)- $(C_{1-6}$  alkyl);  $(C_{1-6}$  alkyl); benzoyl; benzoyl; substituted as herein defined; carbamoyl; CO-NHR<sup>7</sup>; COOR<sup>7</sup>;  $(CH_2)_pOR^a$  where  $R^a$  is  $C_{1-6}$  alkyl or phenyl, and p is an integer from 1 to 5;  $(CH_2)_nCOOR^6$  where n is 0, 1 or 2; or  $(C_{1-6}$  acyloxy)- $(C_{1-6}$  alkoxy) carbonyl;

M, if included in R², R³, R⁴ or R⁵ is (a) -OR¹⁶; (b) halogen; (c) -CF₃; (d) -SR¹⁶; (e) COOR⁶; (f) -NH-CO-R⁷; (g) -NR³R⁹; (h) -SOR¹¹ where R¹¹ is C₁-₆ alkyl or C₁-₄ perfluoroalkyl; (i) -SO₂R¹³ where R¹³ is C₁-₆ alkyl or C₁-₄ perfluoroalkyl; (j) -O-CO-R¹⁴ where R₁₄ is H, C₁-₆ alkyl, phenyl or substituted phenyl as herein defined; (k) O-CO-NR³Rȝ; or (1) -CN;

each  $R^{16}$ , independently of the others, is hydrogen;  $C_{1-6}$  alkyl; benzyl;  $(C_{1-6}$  acyloxy) $(C_{1-6}$  alkyl) or  $C_{1-4}$  perfluoroalkyl;

T is hydrogen or  $-OR_{15}$ , where  $R_{15}$  is hydrogen,  $C_{1-6}$  alkyl,  $(C_{1-6}$  alkyl)-acyl, phenylacyl, substituted phenyl-acyl as herein defined, benzoyl or substituted benzoyl as herein defined; and the other variables are as defined in the preceding paragraph.

In a second especially preferred embodiment of the invention, the composition contains a compound of Formula I in which X is O or S,

 $R^1$  is hydrogen,  $C_{1-4}$  alkyl,  $C_{1-4}$  alkylacyl, -( $CH_2$ ) $_pOR^a$  where  $R^a$  is  $C_{1-4}$  alkyl or phenyl and p is 1, 2 or 3, ( $C_{1-4}$  acyloxy)-( $C_{1-4}$  alkyl), ( $C_{1-4}$  alkoxy)carbonyl or ( $C_{1-6}$  acyloxy)-( $C_{1-4}$  alkoxy)carbonyl;

each of  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$ , independently of the others, is hydrogen, halogen, hydroxyl;  $C_{1-3}$  alkyl;  $C_{1-3}$  alkoxy;  $C_{1-3}$  alkylthio;  $C_{1-5}$  acyloxy; benzoyloxy;  $C_{1-3}$  trihaloalkyl;  $C_{1-4}$  aminoalkyl;  $C_{1-5}$  acyl; (CH<sub>2</sub>)- $_m$ COOR<sup>5</sup>, where m is 0, 1, 2, 3 or 4 and  $R^6$  is H, phenyl or  $C_{1-6}$  alkyl; or ( $C_{1-4}$  acyloxy)-( $C_{1-4}$  alkoxy)-carbonyl; and T is as defined above.

In a third especially preferred embodiment of the invention, the composition contains a compound of Formula III

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in which

 $R^1$  is H,  $C_{1-4}$  acyl,  $(C_{1-4}$  acyloxy)- $(C_{1-4}$  alkyl), or  $C_{1-4}$  acyloxy)- $(C_{1-4}$  alkoxy)carbonyl;  $R^2$  is halogen;

 $R^3$  is OH,  $C_{1-5}$  acyloxy, benzoyloxy, or  $(C_{1-4}$  acyloxy)- $(C_{1-4}$ alkoxy)carbonyloxy;  $R^4$  is H, OH,  $C_{1-4}$  alkoxy or  $C_{1-4}$  acyloxy and is located at either position 1 or position 2;  $R^5$  is OH,  $C_{1-4}$  alkoxy or  $C_{1-4}$  acyloxy;

T is hydrogen or  $C_{1-4}$  alkoxy.

In these preferred embodiments, a pharmaceutically acceptable sait may be used instead of the compound itself.

Examples of the Formula I compounds useful in the compositions of the present invention are tabulated below. In Table I, the number preceding the R<sup>2</sup>-R<sup>5</sup> and T definitions signifies the groups position on the ring system. Standard abbreviations are used, for example, Ph for phenyl, Bz for benzoyl, Ts for p-toluenesul-fonyl, Me for methyl, Bu for butyl, Et for ethyl and Ac for acetyl.

TABLE I

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15	Compound	a_ x	<u>R</u> 1	<u>R</u> 2	R <sup>3</sup>	_R <sup>4</sup>	<u>R</u> 5	<u> </u>
	1	S	Н	H	Н	Н	н	Н
20	2	s	Me	2-t-Bu	4-t-Bu	н	н	1-0H
	3	s	Me	2-t-Bu	4-t-Bu	H	H	1-0Me
	4	s	Ме	2-t-Bu	4-t-Bu	H	Н	1-0Ac
	5	s	Ac	2-t-Bu	4-t-Bu	H	H	1-0H
25	6	S	н	2-t-Bu	4-t-Bu	H	H	1-0 <b>M</b> e
	7	S	н	2-t-Bu	4-t-Bu	H	н	1-0Ac
	8	0	н	2-t-Bu	4-t-Bu	н	н	1-0H
30	9	s	CH <sub>2</sub> OAc	2-t-Bu	4-t-Bu	H	н	1-0H
	10	s	H Z	1-C1	н .	Н	н	3-0H
	11	s	н	1-C1	н .	Н	н	3-0Ac
35	12	S	н	1-C1	н	H	н	3-0 <b>Me</b>
	131	s	Me	1-C1	н	Н	н	3-0H
	141	s	Жe	1-C1	н	H	н	3-0Ac
	15	s	Ме	1-C1	н	н	н	3-0Me
40	16	s		1-C1	н	н	н	3-0Me
	17	s		1-C1	н	H	н	3-0Ac
	18	0	H 2	1-C1	н	н	н	3-OH
45	10	•						

The symbol 1 next to the number of a compound indicates which compounds are preferred and the symbol 2 next to the number of a compound indicates which compounds are also more preferred. 50

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TABLE I (cont'd)

5	Compound	X	<u>R</u> 1	<u>R</u> 2	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	T
	19	0	Me	1-C1	H	н	H	3-OH
10	20	0	Ме	1-C1	н	Н	H	3-0Ac
	21	0	Me	1-C1	Н	H	Н	3-0Me
	22	0	Ac	1-C1	Н	н	H	3-0Ac
	23	0	CH <sub>2</sub> OAc	1-C1	Н	Н	H	3-0Me
15	24	Se	Ме	1-C1	Н	Н	H	3-0Me
	25	so	н	1-01	Н	Н	H	3-0H
	26	SO	н	1-C1	Н	Н	H	3-0Me
20	27	so	н	1-C1	Н	Н	H	3-0Ac
	28	SO	Ме	1-C1	H	Н	H	3-OH
	29	so	Me	1-C1	Н	Н	н	3-0Ac
25	30	so	Me	1-C1	Н	Н	н	3-0Me
20	31	so <sub>2</sub>	н	1-C1	н	н	н	3-0H
	32	so <sub>2</sub>	Н	1-C1	н	н	H	3-0Ac
	33	so <sub>2</sub>	Н	1-C1	н	Н	н	3-0Me
30	34	so <sub>2</sub>	Me	1-C1	н	н	Н	3-0Ac
	35	so <sub>2</sub>	Me	1-C1	7-0CH <sub>2</sub> CO <sub>2</sub> H	н	Н	3-0Ac
	36	so <sub>2</sub>	Me	1-C1	Н 2 .2	н	н	3-0 <b>Me</b>
35	37 <sup>1</sup>	so <sub>2</sub>	Ac	1-C1	н	н	н	3-OH
	38 <sup>1</sup>	so <sub>2</sub>	Ac	1-C1	Н	н	н	3-0Ac
	39	so <sub>2</sub>	Ac	1-C1	н	Н	Н	3-0Me
40	40	so	Ac	1-C1	н	Н	н	3-OH
	41	so	Ac	1-C1	н	Н	н	3-0Ac
	42	so	Ac	1-C1	н	н	н	3-0Me
40	43		CH <sub>2</sub> OAc	1-C1	н	н	н	3-OH
45	44	SO_	CH_OAc	1-Cl	Н	н	н	3-0Ac
	45	so <sub>2</sub>	CH <sub>2</sub> OAc	1-C1	Н	н	н	3-0Me
	46	S	CH <sub>2</sub> Ph	н	н	Н	н	н
50	47	s	Me	н	Н	Н	н	Н

TABLE I (cont'd)

5	Compound	x	<u>R</u> 1	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	T
	48	S	Ac	H	н	н	н	Н
10	49	S	CH <sub>2</sub> OAc	H	н	Н	Н	Н
	50	0	н	Н	Н	H	Н	н
	51	0	Me	H	Н	Н	н	Н
15	52	0	Ac	Н	H	Н	Н	Н
70	53	Se	H	Н	H	н	Н	H
	54	Se	Me	н	н	н	н	Н
	55	Se	Ac	н	н	Н	Н	Н
20	56	Se	CH <sub>2</sub> OAc	H	Н	Н	Н	н
	57	SO	H	H	H	H	Н	н
	58	so	Ме	Н	Н	Н	Н	н
25	59	so <sub>2</sub>	Ac	н	Н	н	Н	Н
	60	s	н	н	н	H	Н	3OH
	61	s	H	н	н	н	H	3-0Ac
30	62	s	н	н	н	Н	н	3-0 <b>Me</b>
	63	S	Me	н	Н	Н	н	3-0Ac
	64	S	Нe	Н	Н	н	H	3-OH
35	65	S	Me	н	н	Н	н	3-0Me
33	66	S	Ac	H	н	H	H	2-OH
	67	S	Ac	н	н	Н	H	3-0Ac
	68	<b>s</b> .	Ac	н	н	'H	H	3-0 <b>Me</b>
40	69	S	CH <sub>2</sub> OAc	H	Н	Н	H	3-OH
	70	S	CH <sub>2</sub> OAc	Н	Н	H	н	3-0Ac
	71	S	CH <sub>2</sub> OAc		Н	Н	н	3-0Me
45	72	Same as	compounds	60-71 t	ut X=0			
	73 <sup>1</sup>	Same as	compounds	60-71 t	out X=Se			-
	74	s	Н	4-C1	н	H	H	3-OH
50	75	, <b>s</b>	н	4-C1	н	H	H	3-0 <b>Me</b>
	76 <sup>1</sup>	S	н	4-C1	н	н	Н	3-0Ac

5	Compound	<u>x</u>	<u>R</u> 1	<u>R</u> 2	3	_R <sup>4</sup>	<u>R</u> 5	<u> </u>
	77	s	Me	4-C1	н	Н	н	3-OH
	78 <sup>1</sup>	S	Me	4-C1	Н	н	н	3-0Ac
10	79 <sup>1, 2</sup>	s	Ме	4-C1	н	н	H	3-0 <b>Me</b>
	80 <sup>1, 2</sup>	S	Ac	4-C1	н	н	H	3-ОН
	81 <sup>1, 2</sup>	s	Ac	4-C1	Н	Н	H	3-0Ac
15	82 <sup>1</sup>	S	Ac	4-C1	н	н	H	3-0 <b>Me</b>
	83	s	Me	4-C1	Н	н	н	3-0-Bz
	841	S	Me	4-C1	н	H ·	Н	3-OCOCH(Me) <sub>2</sub>
20	85	S	Me	4-C1	Н	H	H	3-0COC(Me)3
20	86 <sup>1, 2</sup>	so <sub>2</sub>	Н	4-C1	н	н	H	3-0H
	87 <sup>1</sup>	so <sub>2</sub>	н	4-OH	н	н	H	3-он
	88 <sup>1, 2</sup>	so <sub>2</sub>	н	4-C1	н	н	н	3-0Ac
25	89	so <sub>2</sub>	н	4-C1	н	н	Н	3-OMe
	90	so <sub>2</sub>	Ме	4-C1	н	н	Н	3-OH
	91	2 S0 <sub>2</sub>	Me	4-C1	Н	н	Н	3-0Ac
30	921	so <sub>2</sub>	Ме	4-C1	н	н	Н	3-0 <b>Me</b>
	93 <sup>1</sup> , <sup>2</sup>	so <sub>2</sub>	Ac	4-C1	н	н	H	3-0H
	941, 2	so <sub>2</sub>	Ac	4-C1	н	н	H	3-0Ac
35	95	so <sub>2</sub>	Ac	4-C1	Н	н	Н	3-OMe
55	96	s s		4-C1	Н	Н	H	H
	97	s	<b>~</b> .	4-C1	Н	н	Н	3-OH
	98	S	2	4-C1	H	н	Н	3-0Ac
40	99		CH <sub>2</sub> OAc			Н	Н	3-0 <b>Me</b>
	100	SO.	CH_OAc	4-C1	Н	н	H	3-OH
	101	2 80	CH <sub>2</sub> OAc CH <sub>2</sub> OAc	4-C1	H	н	н	3-0Ac
45	102		CH <sub>2</sub> OAc	A-C1	н	н	н	3-0Me
70	102	SO <sub>2</sub>	compounds			44		J-0116
	103		compounds					
60	105		compounds			7-C1		

5	Compound	X		<u>R</u> 1	_R <sup>2</sup>	R <sup>3</sup>	<u>R</u> 4	<u>R</u> 5	<u> </u>
	106	Same	as	compound	105 but	X=0			
10	107	Same	as	compounds	74-103	but R <sub>4</sub> i	s 7-0M	•	
	108	Same	as	compound	107 but	X=0			
	109	Same	as	compounds	74-103	but R <sub>4</sub> i	s 7-(C	l-C alk	y1)
	110	Same	as	compound	109 but	<b>X=</b> 0			
15	111	Same	as	compounds	74-103	but R <sub>4</sub> i	s 7-(C	OMe)	
	112	Same	as	compound	111 but	X=0			
	113	Same	as	compounds	74-103	but R <sub>4</sub> i	s 7-[((	H <sub>2</sub> ) _COO	R], wherein
20		m is							
	114	Same	as	compound	113 but	X=0			
	115	Same	as	compounds	74-103	but R <sub>4</sub> i	s 9-Cl		
25	116	S		Н	4-Et	Н	H	H	3-0H
	117	S		Me	4-Et	H	H	н :	3-OCOCH <sub>2</sub> Ph
	118	S		Me	4-Et	H	H	н	3-0Ac
	119	S		Me	4-Et	H	H	H	3-0 <b>Me</b>
30	120	S		Н	4-0Et	Н	H	Н	3-0H
	121	S		H	4-0Et	H	H	н	3-0Me
	122	S		Ме	4-OEt	H	H	н	3-0Me
35	123	S		Не	4-0Et	н	H	н	3-0Ac
	124	s		Н	2-0Et	7-0Et	H	Н	3-0H
	125	S		Н	2-0Et	7-0Et	H	н	3-0Me
40	126	S		Me	2-0Et	7-OEt	H	н	3-0 <b>Me</b>
	127	S		Me	2-0Et	7-0Et	H	H	3-0Ac
	128	s		н	Н	Н	H	H	3-0AC
45	129	S		Me	н	н	H	3-Ac	Н
45	130	S		Ac	H	H	H	3-Ac	3-0Ac
	131	S		н	7-Ac	н	H	3-Ac	н
	132	s		Me	7-Ac	н	н	3-Ac	Н
50	133	S		Ac	7-Ac	н	H	3-Ac	Н

TABLE I (cont'd)

5	Compound	x	<u>R</u> 1	R <sup>2</sup>	R <sup>3</sup>	_R <sup>4</sup>	<u>R</u> 5	T
	174	s	CH 04c	7-Ac	н	н	3-Ac	Н
	134		CH <sub>2</sub> OAc H	2-Me	4-C1	н	H	3-0H
10	135	S		2-Me 2-Me	4-G1	н	H	3-OAc
	136	S	Me 	2-me 7-Me	2-Me	H	н	3-0H
	137	s	H	7-me 7-Me	2-Me 2-Me	H	H	3-0Ac
15	138 139 <sup>1</sup>	s	Me	2-0Et	4-C1	н	н	3-0H
75		s	H M-	2-0Et 2-0Et	4-C1	н	н	3-0Ac
	140	S	Me 		4-C1	н	н	3-0H
	141	S	H 	2-S-n-Bu	4-C1			3-0Ac
20	142	<b>S</b>	Ке	2-S-n-Bu		H	H H	3-OAc
	143	S	Me	4-S-n-Bu	H	H 		
	144	S	Me	2-0-Me	4-Br	H	H	3-0Ac
25	145	S	Ме	2-0-Me	4-C1	H	H 	3-0Ac
23	146	S	Ме	2-0-Me	4-Br	Н	H	3-OH
	1471	S	Н	2-0 <b>-Me</b>	3-OH	Н	H	7-0Me
00	148	S	Н	1-OMe	3-OH	Н	н	7-0Me
30	149	s	Н	2-0 <b>Me</b>	3-OH	1-Br	Н	7-0 <b>Me</b>
	150	S	Н	1-0Me	3-OH	2-Br	Н	7-0 <b>Me</b>
	1511	S	Н	1-0 <b>Me</b>	3-OH	4-Br	H	7-0 <b>Me</b>
36	152	s	H	1-0Me	3-0H	2-C1	H	7-0 <b>Me</b>
	1531	S	H	1-0Me	3-0H	4-C1	H	7-0 <b>Me</b>
	154	S	Н	2-0 <b>Me</b>	3-0H	1-G1	Н	7-0Me
40	155	S	Н	2-0Me	3-0H	4-C1	H	7-0Me
	156	S	н	2-0Et	3-0H	1-Br	H	7-0Et
	157	S	н	2-0Et	3-0H	4-Br	H	7-OEt
45	158	S	н	2-0Et	3-0H	1-C1	H	7-OEt
45	1591	s	н	2-0Et	3-0H	4-C1	Н	7-0Et
	160	S	Н	2-0 <b>Me</b>	3-0H	1-Br	7-0Me	9-0Me
	161	S	н	2-0 <b>Me</b>	3-0H	4-Br	7-0Me	8-OMe

# TABLE I (cont'd)

5	Compound	X	<sub>R</sub> 1	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	<sub>R</sub> 5	Ţ
	162]	S	Н	2-0Me	3-0H	4-F	н	7-0Me
10	163	\$	н	2-0Me	3-0H	4-CF <sub>3</sub>	н	7-0Me
,,	164 <sup>1</sup>	s	н	2-0Me	3-0H	4-Br	н	7-OEt
	165 <sup>1</sup>	s	Н	2-0Me	3-OH	4-C1	Н	7-0Et
	166	S	н	2-0Me	3-OH	4-F	Н	7-0Et
15	167	S	н	2-0Me	3-OH	4-I	Н	7-OMe
	168	S	Н	2-0Me	3-0H	4-CF <sub>3</sub>	H	7-0Et
	169	s	Н	2-0Et	3-0H	4-8r	H	7-OMe
20	170	S	н	2-0Et	3-0H	4-C1	Н	7-0 <b>Me</b>
	171	S	Н	2-0Et	3-OH	4-F	Н	7-OMe
	172	S	н	2-0Et	3-OH	4-CF <sub>3</sub>	H	7-OMe
25	173	S	Н	1-OMe	2-0 <b>Me</b>	3-OH	4-8r	70Me
	174	S	Н	1-0Me	3-0H	Н	Н	20Me
	175	5	Н	1-0Me	3-0H	4-Br	Н	2-0Me
30	176	Same as	compounds	147-175	but X=0			
	177	Same as	compounds	147-175	but X=SO	2		
·	178	S	н	2-SMe	3-0H	4-Br	Н	7-OMe
	179	S	н	2-0Me	3-OH	4-8r	7-SMe	H
35	180	50 <sub>2</sub>	н	2-S0 <sub>2</sub> Me	3-0H	4-8r	Н	7-0 <b>Me</b>
	181	Same as	compounds	147-175	but X=S0	)		
	182	S	Н	4-C1	Н	Н	Н	3-08z
40	183	S	Н	4-C1	H	н	H 3-0	COCH(Me) <sub>2</sub>
	184	S	Ac	H	н	7-F	н	3-0Ac
	185	\$	Me	Н	Н	7-Me	н	3-0Me
45	186	S	Н	Н	H	7-F	Н	3-OAc
	187	S	Me	H	н	9-C1	Н	3-0Me
	188	S	Me	H	Н	9-C1	Н	3-0Ac
50	189	S	Me	Н	Н	7-Me	Н	3-0Ac

TABLE I (cont'd)

5	Compound	<u>x</u>	R <sup>1</sup>	<u>R</u> 2	R <sup>3</sup>	R <sup>4</sup>	<sub>R</sub> 5	T
	1901	s	н	Н	н	9-C1	H	3-0Ac
	191 <sup>1</sup>	S	н	Н	4-CF <sub>3</sub>	Н	н	3-0Ac
10	192	s	н	н	4-C1	н	н	3-0Ts
	1931	S	Ac	Н	4-C1	7-F	Н	3-0Me
	1941	S	Ac	Н	4-C1	7-F	Н	3-0H
15	195 <sup>1</sup>	S	Ме	H	4-C1	7-F	Н	3-0Me
	1961	so	н	H	H	H	Н	3-0Ac
	1971,2	so <sub>2</sub>	Н	Н	Н	H ·	н	3-0Ac
20	1981,2	so <sub>2</sub>	H	Н	Н	H	Н	3-OH
	199 <sup>1</sup>	so <sub>2</sub>	н	Н	Н	7-F	н	3-0Ac
	2001	so <sub>2</sub>	Н	Н	4-C1	H	Н	3-0Ts
	2011	s	н	1-0Me	2-OMe	4-Me	Н	3-OH .
	2021	s	H	1-0Me	2-0 <b>Me</b>	4-Me	Н	3-0Ac
	203	so <sub>2</sub>	Н	1-0Me	2-0Me	4-Me	н	3-OH
	204	so <sub>2</sub>	H	4-0 <b>Me</b>	н	н	Н	3-OH
30	2051	s	Н	2-0 <b>Me</b>	3-0H	4-Br	7-0Me	H
	2061	S	H	2-0Me	3-0Ac	4-Br	7-0Me	H
	2071	S	Н	2-0Me	3-0Ac	4-C1	7-0Me	н
35	208	so <sub>2</sub>	н	2-0Me	3-0H	4-Br	7-0Me	н
	209 <sup>1</sup>	s	H	2-0Me	3-0Ac	7-0Me	4-Br	н
	2101	S	Н	2-0Me	3-0Ac	7-0Me	4-Br	н
	211	S	н	2-0Me	3-0Bz	7-0 <b>Me</b>	4-Br	н
40	212	S	Нe	2-0Me	3-OMe	7-0Me	4-Br	Н
	2131	S	н	2-0Me	3-0 <b>Me</b>	7-0 <b>Me</b>	4-Br	Н
	2141,2	S	Ac	2-0Me	3-0Ac	7-0 <b>Me</b>	4-Br	H
45	215 <sup>1,2</sup>	S	Ac	2-0Me	3-OH	7-0Me	4-Br	н
	216	S	Ac	2-0Me	3-0Me	7-0Me	4-Br	н
	2171	S	Мe	2-0Me	3-0Ac	7-OMe	4-Br	Н

# TABLE I (cont'd)

5	Compound	x	R <sup>1</sup> R <sup>2</sup>		<u>R</u> 3 <u>R</u>	l	<u>R<sup>S</sup> T</u>	
•	<u>odipodina</u>	<u> </u>						
	218	s	Me	2-0Me	3-OH	7-0Me	4-8r	Н
10	219	so <sub>2</sub>	н	2-0Me	3-OH	7-0 <b>Me</b>	4-Br	Н
70	2201	\$0 <sub>2</sub>	Н	2-OMe	3-0Ac	7OMe	4-8r	Н
	221	so	н	2-0Me	3-0Ac	7-0Me	4-Br	H
	222	50	н	2-0Me	3-OAc	7- <b>0Me</b>	4-Br	Н
15	223	SO	H	2-0Me	3-QAc	7-OMe	4-8r	Н
	224	s	н	2-0 <b>M</b> e	3-000 <sub>2</sub> Me	4-8r	7-0Me	н
	225	s	н	2-0 <b>Me</b>	3-000 <sub>2</sub> Et	4-8r	7-0Me	H
20	226 1,2	S	н	2-OMe	3-000 <sub>2</sub> CH (Me) 0Ac	4-Br	7-Offe	Н
	227	S	н	2-0Me	3-000 <sub>2</sub> CH (Me) 0Ac	4-C1	7-OMe	Н
	228	S	∞ <sub>2</sub> #e	2-0Me	3-OH _	4-8r	7-0Me	H
25	229	s	∞_Et	2-0 <del>Me</del>	3-OH	4-8r	7-0Me	H
	2301,2	s	CO <sub>2</sub> CH (Me) OAc	2-0Me	3-OH	4-8r	7-OMe	H
	231	s	CO_CH (Me) QAc	2-0Me	3-OH	4-C1	7-OMe	H
	232	s	CO_CH(Me)OAc	2-0Me	3-OH	4_F	7-OMe	H
30	233 <sup>1,2</sup>	s	∞2cH(Me)OAc	2-0Me	3-0Ac	4-Br	7-OMe	Н
	234	s	CO <sub>2</sub> CH(Me)OAc	2-OMe	3-000 <sub>2</sub> CH (Me) 0Ac	4-8r	7-0 <del>11e</del>	н
	235 <sup>1,2</sup>	0	Ac	2-OMe	3-OH	4-Br	7-0Me	н
35	236 1,2	0	Ac	2-OMe	3-0Ac	4-Br	7-OMe	Н
	2371,2	0	CO <sub>2</sub> CH(Me)OAc	2OMe	3-0H	4-Br	7-0Me	H
	238	0	CO_CH(Me)OAc	2-OMe	3-0Ac	4-8r	7-OMe	Н
40	239	S	H	2-OMe	3-0H	4 <u>-</u> 8r	7-Me	Н
	240	\$	н	2-OMe	3-0Ac	4-8r	7- <b>He</b>	H
	241	S	н	2-OMe	3-OH	4-Br	7-F	H
45	242	\$	н	2-OM6	2-QAC	4-Br	7-F	Н

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# TABLE I (cont'd)

		<u>x</u>	<u>R</u> 1_	<u>R</u> 2	<u>R</u> 3_	<u>R</u> 4	<u>R</u> 5	<u>I</u>
5								
	243	S	н	н	Н	н	н	OCOEt
	244	\$	Н	2-C1	3-C1	н	н	000-n-Pr
10	245	\$	Н	អ	4-C1	н	Н	000-n-Bu
	246	5	н	1-Me	H	Н	н	Н
	247	S	н	2-CF <sub>3</sub>	н	Н	н	H
15	248	S	Н	2-Et	Н	н	H	Н
10	249	S	н	Н	3-C1	7OMe	H	н
	250	\$	H	Н	3-C1	7-C1	Н	Н
	251	S	н	H	3-NO <sub>2</sub>	H	7-NO <sub>2</sub>	H
20	252	S	н	3-NMe <sub>2</sub>	н	H	7-HMe <sub>2</sub>	н
	253	S	н	1-OH	Н	H	H	н
	254	S	н	3-0Ac	7 <b>-</b> F	Н	H	н
25	255	S	н	3-CH <sub>2</sub> COMe	4-C1	н	Н	Н
	256	S	Н	3-OCOCHMe <sub>2</sub>	н	4-C1	H	н
	257	S	Ac	3-0 <del>1</del>	4C1	H	H	Н
50	258	0	Н	2-CF <sub>3</sub>	н	Н	H	Н
30	259	S	Me	Н	3-0Me	H .	4-C1	H
	260 <sup>1</sup>	<sup>SO</sup> 2	н	4-C1	3-OH	н	Н	Н
	261	5	Me	7 <b>-</b> F	4-C1	3-OMe	H	H
35 -	262	\$	Me	3-0Me	7He	Н	Н	Н
	263	\$	Ac	4_C1	H	H	H	н
	264	S	Ac	3-0Ac	4-C1	Н	H	н
40	265	<sup>50</sup> 2	Ac	4-C1	H	H	H	3-OH
	266	s0 <sub>2</sub>	Ac	4-C1	H	H	Н	3-0Ac
	267	S0 <sub>2</sub>	Ac	4-8r	Н	Н	H	3-0Ac
		-						

# TABLE I (cont'd)

5		<u>x</u>	<u>R</u> 1_	<u>R</u> 2_	<u>R</u> 3_	<u>R</u> 4_	<u>8</u> 5	Ī
	268	so <sub>2</sub>	CO <sub>2</sub> CH(Me)OAc	4-C1	H	н	н	3-OH
10	269	so <sub>2</sub>	Н	4 <b>-</b> C1	н	H 3-00	CO <sub>2</sub> CH(Me)OAc	H
15	270	0	Ac	4-C1	н	Н	н	3-0Ac
	271	0	CO <sub>2</sub> CH (Me) OAc	4-C1	н	н	н	3-OH
20	272	0	CO <sub>2</sub> CH(Me)OAc	4-C1	н	н	н	3-0Ac
25	273	0	Н	4-C1	н	н 3-0	00 <sub>2</sub> CH(Me)OAc	н
	274	s	CH <sub>2</sub> OAc	4-C1	н	н	H	3-0Ac
30	275 1,2	\$	CH(Me)OAc	4C1	н	Н	н	3-0Ac
35	276 <sup>1</sup>	s	н	2-OMe	3-OH	7-OH	н	Н
00	277	S	Н	2-0Me	3-OH	7-OH	4–Br	Н
40	278	s	Н	2-OMe	3-0Ac	7-OH	4-8r	Н
	279	S	н	2-0Me	3-0Ac	7-0Ac	4-8r	н

# TABLE I (cont'd)

5	Compound	x	<u>R</u> 1_	<u>R</u> 2_	<u>8</u> 3_	<u>R</u> 4_	ß_	Ī
	280 <sup>1,2</sup>	s	Ac	2OMe	3-OH	7-0H	4-8r	н
	281	S	Ac	2-0Me	3-QAc	7-OH	4-8r	H
10	282 1	s	Ac	2-0Me	3-OAc	7-0Ac	4-Br	н
	283 <sup>1,2</sup>	\$	Ac	2-0Me	3-OH	7-0Ac	4-Br	H
	284 <sup>1,2</sup>	so <sub>2</sub>	Ac	2OMe	3-OH	4-8r	7-0Me	н
15	285 <sup>1</sup>	so <sup>5</sup>	CO <sub>2</sub> CH(Me)OAc	2-0Me	3-0Ac	4-Br	7OMe	н
20	286 <sup>1</sup>	so <sub>2</sub>	Ac	2-0 <b>%</b> e	H 	4-8r	70Me	н
25	287 1,2	so <sub>2</sub>	Ac	2-0Me	3OAc	4-8r	7OMe	н
	288 <sup>1,2</sup>	so <sub>2</sub>	∞ <sub>2</sub> CH(Me)OAc	2-0He	3~OH	4-8r	7~0Me	н
30	289 <sup>1,2</sup>	S	Ac	2-0Et	3-0Ac	4-C1	н	н
	290 <sup>1,2</sup>	S	Ac	2-0Et	3-OH	4_C1	н	H
	291	s	Me	Н	7-AC	н	н	3-OMe
35	2921	\$	Ме	н	н	7-F	H	3-OMe
	293	S	Ac	H	н	7-F	н	3-0Me
	294 <sup>1</sup>	S	Ac	Н	Н	7 <b>-</b> F	Н	3-OH

	Compound	X	<u>R</u> 1_	<u>R</u> 2_	<u>R</u> 3	<u>R</u> 4_	<u>8</u> 5_	Ī
5	295	s	н	2-OMe	4-I	7-0Me	H	3-OH
	296	s	H	2-OMe	4-CN	7-OMe	H	3-OH
	297	S	H	2-0Et	4-Br	7-OEt	H	3-OH
10	298	S	н	2-0Et	4-C1	7-0Et	H	3-OH
10	299	S	H	2-0Me	4-Br	7-OEt	H	3-OH
	300	s	H	2-OMe	4-C1	7-OEt	H	3-OH
	301	S	Н	2-OMe	4-F	7-OEt	H	3-OH
15	302	S	H	2-0Et	4-Br	7-OMe	H	3-OH
	303	s	H	2-0Et	4-Cl	7-OMe	H	3-OH
	304	s	Н	2-0Et	4-F	7-OMe	H	3-OH
20	305	S	Н	2-OEt	4-CF <sub>3</sub>	7-0Me	Н	3-OH

The compounds of the Formula I have unexpected activity as inhibitors of the mammalian biosynthesis of both leukotriene B<sub>4</sub>, as well as leukotrienes C<sub>4</sub>, D<sub>4</sub>, E<sub>4</sub> and F<sub>4</sub>, the active elements of slow reacting substance of anaphylaxis (SRS-A). This inhibition of the biosynthesis of leukotrienes indicates that the compositions would be useful to treat. prevent or ameliorate, in mammals and especially in humans 1) pulmonary conditions including diseases such as asthma, 2) allergies and allergic reactions such as allergic rhinitis, contact dermatitis. allergic conjunctivitis and the like, 3) inflammation such as arthritis, 4) pain, 5) skin conditions such as psoriasis and the like and 5) cardiovascular conditions such as angina and the like.

Representative compounds of Formula I have been tested using one or more of the following assays to determine their mammalian leukotriene biosynthesis inhibiting activity and other relevant activities.

### Mouse Macrophage Assay

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Mouse peritoneal macrophages were treated sequentially with arachidonic acid (labelled with tritium): the compound being evaluated as an inhibitor, and a stimulator (zymosan). Metabolites derived from arachidonic acid (PGE<sub>2</sub>, 6-Keto PG-F<sub>1@</sub> and Leukotriene C<sub>4</sub>) were separated from the incubation medium by extraction and chromatography, and then quantitated by determining the amount of radioactivity (cpm) associated with each of them. Inhibitors caused a reduction in the amount of radioactivity (cpm) associated with a given metabolite. (This protocol is identical to that described in the reference except that the radioactivity herein associated with the LTC<sub>4</sub> was determined by counting an aliquot of the final aqueous solution directly rather than chromatographing it first).

Reference: Humes. J.L. et al., J. Biol. Chem. 257, 1591-4 (1982).

## 5 Antigen Challenge 'in vitro' Assay

Male guinea pigs weighing 300-350 g were sensitized by injecting (i.p.) 0.5 ml of a suspension containing 0.4 mg of egg albumin (Ovalbumin, Grade V, Sigma Chemical Co.) and 4.0 g aluminum hydroxide in 19.6 ml of saline. Two weeks were permitted for sensitization to occur.

Three sensitized guinea pigs were stunned and exsanguinated. The tracheas were removed, freed of adhering tissue and divided longitudinally by cutting through the cartilaginous tissue directly opposite the muscle insertion. Each opened trachea was then transected between every second cartilage. Four of the cut sections were tied together, end to end in a series with No. 0.7 silk thread ensuring that the tracheal muscles were all in the same vertical plane. Thus, each chain consisted of tissue from three different animals.

The chain so formed was then suspended under 1 g of tension (by silk ties at each end) in a 20 ml

organ bath containing 10 ml of modified  $^1$  Krebs-Henseleit buffer solution gassed with 95%  $\rm O_2$  and 5%  $\rm CO_2$  at 37  $^{\circ}$  C. Mepyramine (0.55  $\mu \rm g/ml$ ) and indomethacin (2.67  $\mu \rm g/ml$ ) were added to the buffer to avoid the contribution of histamine receptors and cyclooxygenase products to the contraction. To record responses one end of the tracheal chain was attached to a Gould Statham UC-2 force displacement transducer which was connected to a Beckman Type R-dynograph. The preparations were allowed to equilibrate for one hour during which time the tissues were automatically washed (10 ml volume displacement) every 6 minutes.

After the equilibration period the tissues were primed with methacholine (3  $\mu$ g/1ml; 1.5 x 10<sup>-5</sup>M), washed and allowed to recover to baseline. The tissues were treated again with a second dose of methacholine, washed, allowed to return to baseline and washed for an additional hour.

Two chains were used as a control. These were incubated in a concentration of egg albumin sufficient to induce an average contraction of 50-80% of the methacholine response.

Each compound to be tested was added to two other baths (at a final concentration in each bath of 10  $\mu$ g/ml or lower) 15 minutes prior to challenging the fresh chains with egg albumin.

The response of the challenged tissue was expressed as a percentage of the methacholine maximum. The % inhibition for each compound was then calculated. Compounds which at 10  $\mu$ g/ml (final concentration) inhibited the egg albumin response by 50% or more were retested at a lower concentration.

### RAT POLYMORPHONUCLEAR LEUKOCYTE (P.M.N.) Assay

Rats under ether anesthesia are injected (i.p.) with 8 ml of a suspension of sodium caseinate (6 grams in ca. 50 ml water). After 15-24 hours the rats are sacrificed (CO<sub>2</sub>) and the cells from the peritoneal cavity are recovered by lavage with 20 ml of buffer (Eagles MEM containing 30 mM HEPES adjusted to pH 7.4 with NaOH). The cells are pelleted (350 x g, 5 min.), resuspended in buffer with vigorous shaking, filtered through lens paper, recentrifuged and finally suspended in buffer at a concentration of 10 cells/ml. A 500 µl aliquot of PMN suspension and test compound are preincubated for 2 minutes at 37° C, followed by the addition of 10 µM A-23187. The suspension is stirred for an additional 4 minutes then bloassayed for LTB<sub>4</sub> content by adding an aliquot to a second 500 µl portion of the PMN at 37° C. The LTB<sub>4</sub> produced in the first incubation causes aggregation of the second PMN, which is measured as a change in light transmission. The size of the assay aliquot is chosen to give a submaximal transmission change (usually -70%) for the untreated control. The percentage inhibition of LTB<sub>4</sub> formation is calculated from the ratio of transmission

change in the sample to the transmission change in the compound-free control.

Results from the assays described above for several compounds of Formula i are shown in Table II.

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glucose-2.1 (120);(11);solution in grams/liter and (mM): NaCI-6.87 1 modified Krebs (0.5); KH₂PO₄-0.16 (2.5); MgSO<sub>4</sub>.7H<sub>2</sub>O-O.11 (4.72);CaCl<sub>2</sub>-0.28 NaHCO<sub>3</sub>-2.1 (25);KCI-0.32 (1.2); pH of bathing solution- $7.35 \pm 0.05$ 



# TABLE II ASSAY RESULTS

5					In Vitro Antigen
					Challenge % Inhibition
10			Macrophage	P.M.N.	at concentration
			1C <sub>50</sub>	IC <sub>50</sub>	in parenthesis
		Compound	(µg/ml)	(ug/ml)	(µg/ml)
15		u			
20	1		0.06	0.4	100% (10)
25	2	H C1	0.04	-	-
30	3	S C1	0.01-0.1	0.05-0.5	37% (10)
35 40	4	S CH3	5	-	76% (10)
45	5	S CF3	0.1	-	7% (10)

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5 6 0.1-1 0.016 100 (10) 47 (1) 10 0.01-0.1 0.005 60 (10) 15 0.2 60 (10) 8 20 25 0.005 97 (3) 30 10 0.1-1 14 (3) 35 92% 11 0.1 100 (10) 40 62 ( 1) 45

 $^{1}$  Percentage inhibition at 5  $\mu$ g/ml.

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55

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60 (1)

0.01-0.1

5 H 22 (10) 0.12 10 1 (10) 0.01-0.1 15 20 21 (10) 0.0016-0.008 OMe 25 16 0.01 30 5 35 3 (10) 40 0.05-0.5 18

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0.005

				•	
5 10	20	H N N S Me	-	0.005-0.05	65 (10)
15	21	AC N	5	-	-
20	22	AC NOME	1.0	1.0	91 (10)
25 30	23	CF3	-	0.05-0.5	40 (3)
35	24	, A LANGE OF THE PARTY OF THE P	0.1	5	88% (1)
40	25	C1 Me N SOAc	-	0.5	1-9% (3)
45	26	Me N. OMe	1	5	3% (10)
50		C1			

In addition to the assay results described in Table II, the following assays were employed to determine the effectiveness of selected compounds of Formula I as antiasthma and analgesia agents.

### Asthmatic Rat Assay

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Rats were obtained from an inbred line of asthmatic rats. Both female and male rats from 200 to 300 g were used.

Egg albumin (EA), grade V, crystallized and lyophilized, was obtained from Sigma Chemical Co., St. Louis. Bordetella pertussis vaccine, containing 30 x 10<sup>9</sup> killed bacteria per ml was obtained from the institut Armand-Frappier, Laval des Rapides, Quebec. Aluminum hydroxide was obtained from the Regeis Chemical Company, Chicago.

The challenge and subsequent respiratory recordings were carried out in a clear plastic box with internal dimensions 10 x 6 x 4 inches. The top of the box was removable; in use, it was held firmly in place by four clamps and an airtight seal was maintained by a soft rubber gasket. Through the center of each end of the chamber a Devilbiss nebulizer (No. 40) was inserted via an airtight seal and each end of the box also had an outlet. A Fleisch No. 0000 pneumotachograph was inserted into one end of the box and coupled to a Grass volumetric pressure transducer (PT5-A) which was then connected to a Beckman Type R Dynograph through appropriate couplers. While aerosolizing the antigen, the outlets were open and the pneumotachograph was isolated from the chamber. The outlets were closed and the pneumotachograph and the chamber were connected during the recording or the respiratory patterns. For challenge, 2 ml of a 3% solution of antigen in saline was placed into each nebulizer and the aerosol was generated with air from a small Potter diaphragm pump operating at 10 psi and a flow of 8 liters/minutes.

Rats were sensitized by injecting (s.c.) 1 ml of a suspension containing 1 mg EA and 200 mg aluminum hydroxide in saline. Simultaneously, they received an injection (i.p.) of 0.5 ml of B. pertussis vaccine. They were used between days 14 and 18 postsensitization. In order to eliminate the serotonin component of the response, rats were pretreated intravenously 5 minutes prior to aerosol challenge with 30 gm kg<sup>-1</sup> methylserzide. Rats were then exposed to an aerosol of 3% EA in saline for exactly 1 minute, then their respiratory profiles were recorded for a further 25-30 minutes. The duration of continuous dyspnoea was measured from the respiratory recordings.

Compounds were generally administered either intraperitoneally 1 hour prior to challenge or orally 1-1/2 hours prior to challenge. They were either dissolved in dimethylsulfoxide or suspended in 0.1% methocal and 0.5% Tween 80. The volume injected has 2 ml kg<sup>-1</sup> (intraperitoneally) or 10 ml kg<sup>-1</sup> (orally). Prior to oral treatment rats were starved overnight. Their activity was determined in terms of their ability to decrease the duration of symptoms of dyspnoea in comparison with a group of vehicle-treated controls. Usually, a compound was evaluated at a series of doses and an ED<sub>50</sub> was determined. This was defined as the dose (mg/kg) which would inhibit the duration of symptoms by 50%.

### PAF-Induced Hyperalgesia Assay

Female Sprague-Dawley rats, 35-40 g were fasted overnight. Platelet activating factor, PAF, (L-lecithin B-acetyl O-alkyl) 1  $\mu$ g/0.1 ml was given by subplantar injection in the rat paw. The compounds to be evaluated were homogenized in aqueous Vehicle (0.9% benzyl alcohol, 0.5% Tween 80 and 0.4% methylcellulose) and administered orally in a volume of 0.1 ml, 30 minutes prior to PAF.

Animals were tested 1, 2, 3 and 4 hours after PAF administration. The vocalization threshold, defined as the pressure (mm Hg) needed to evoke a squeak response, was recorded for both the injected and contralateral paw. No animal was subjected to pressure greater than 60 mm Hg. Hyperalgesia is defined as

a decrease in vocalization threshold as compared to a normal paw. Percent inhibition of hyperalgesia was calculated as the proportion of animals with vocalization thresholds greater than 200% of controls.

Results for the assays described above for several compounds of Formula I are shown in Table III.

# ASSAY RESULTS

TABLE III

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Asthmatic

PAF Induced

Rat Assay

Hyperalgesia Assay

% inhibition

% inhibition

Compound

and dose

and dose

20

25

53% 50% 
$$(0.5 \text{ mg kg}^{-1} \text{ p.o.})$$
 (3 mg kg $^{-1}$  p.o.)

$$(3 \text{ mg kg}^{-1} \text{ p.o.})$$

30

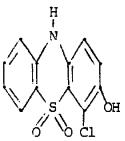
35

70% (3 mg kg<sup>-1</sup> p.o.)

(3 mg kg<sup>-1</sup> p.o.)

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59%

59%  $50\sqrt{8}$  (1.5 mg kg<sup>-1</sup> p.o.) (1.2 mg kg<sup>-1</sup> p.o.)

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## TABLE III (cont'd)

5 Me 50% 50% 50% 50% (0.2 mg kg<sup>-1</sup> p.o.) (0.016 mg kg<sup>-1</sup> p.o.)

Me
N
42%
(3 mg kg<sup>-1</sup> p.o.)

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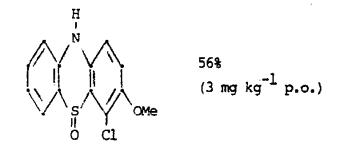
25
Me
N
N
O 35%
70%
Me (3 mg kg<sup>-1</sup> p.o.) (1 mg kg<sup>-1</sup> p.o.)

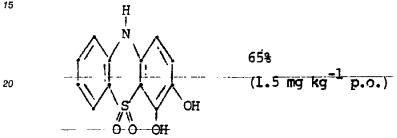
Me

58%

30%

(3 mg kg<sup>-1</sup> p.o.) (1 mg kg<sup>-1</sup> p.o.)





The cytoprotective activity of a compound may be observed in both animals and man by noting the increased resistance of the gastrointestinal mucosa to the noxious effects of strong irritants, for example, the ulcerogenic effects of aspirin or indomethacin. In addition to lessening the effect of non-steroidal anti-inflammatory drugs on the gastrointestinal tract, animal studies show that cytoprotective compounds will prevent gastric lesions induced by oral administration of strong acids, strong bases, ethanol, hypertonic saline solutions and the like.

Two assays can be used to measure cytoprotective ability. These assays are; (A) an ethanol-induced gastric ulcer assay and (B) an indomethacin-induced ulcer assay.

### A. Ethanol-Induced Gastric Ulcer

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Twenty-four hour fasted Sprague-Dawley (S.D.) rats are perorally (p.o.) dosed with 1.0 ml absolute ethanol. Fifteen to thirty minutes prior to ethanol administration, groups of rats each receive either an aqueous vehicle (aqueous methylcellulose 5% wt.) or the test compound at various doses perorally. One hour later, the animals are sacrificed and stomach mucosae are examined for resulting lesions.

### B. Indomethacin-Induced Ulcer Assay

Indomethacin, 10 mg/kg p.o., is used to induce ulcers in 24 hour fasted S.D. rats. Fifteen minutes prior to indomethacin administration, groups of rats each receive either an aqueous vehicle (5% by weight methylcellulose) or the test compound at various doses perorally. Four hours later the animals are sacrificed and stomach mucosae are examined for resulting ulcers.

The pharmaceutical compositions will contain a sufficient amount of a compound of Formula I in a dosage form suitable for inhibiting the mammalian biosynthesis of leukotrienes or, for the treatment desired. The effective concentration of a Formula I compound in the composition will vary as required by the nature and the severity of the condition to be treated, the particular compound selected, the mode of administration, the dosage form and the pharmacological effect and level desired.

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a leukotriene antagonist. For example, oral, rectal, transdermal, parenteral, intramuscular, intravenous and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules and the like.

A general daily dosage of a Formula I compound for anti-asthmatic, anti-allergic, anti-inflammatory and, generally, uses other than cytoprotection will range from about 10  $\mu$ g/kg to 20 mg/kg of body weight. A preferred daily dosage range is from 50  $\mu$ g/kg to 20 mg/kg and a most preferred dosage range is from 100  $\mu$ g/kg to 10 mg/kg.

The exact amount of a compound of the Formula I to be used as a cytoprotective agent will depend on, infer alia, whether it is being administered to heal damaged cells or to avoid future damage, on the nature of the damaged cells (e.g., gastro-intestinal ulcerations vs. nephrotic necrosis), and on the nature of the causative agent. An example of the use of a compound of the Formula I in avoiding future damage would be co-administration of a compound of the Formula I with a non-steroidal anti-inflammatory drug (for example, indomethacin) that might otherwise cause such damage. For such use, the compound of Formula I is administered from 30 minutes prior up to 30 minutes after administration of the NSAID. Preferably, it is administered prior to or simultaneously with the NSAID.

The effective daily dosage level for compounds of Formula I inducing cytoprotection in mammals, especially humans, will generally range from 0.002 mg/kg to 100 mg/kg, preferably from 0.02 mg/kg to 30 mg/kg. The dosage may be administered in single or divided individual doses.

The pharmaceutical compositions of the present invention comprise a compound of formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include sodium, potassium, lithium, ammonium, calcium, magnesium, ferrous, zinc, copper, manganous, aluminum, ferric, manganic salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, N,N¹-dibenzyl-ethylenediamine, morpholine, N-ethyl morphine, and polyamine resins.

When the compound of Formula I is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include hydrochloric, hydrobromic, sulfuric, nitric, isethionic, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, acetic, benzoic, camphorsulfonic, citric, fumaric, gluconic, glutamic, lactic, malic, maleic, mandelic, mucic, pamoic, pantothenic, phosphoric, succinic and tartaric acids. Particularly preferred are hydrochloric, hydrobromic, citric, maleic, phosphoric, sulfuric and tartaric acids. For a helpful discussion of pharamceutical salts see S.M. Berge et al., Journal of Pharmaceutical Sciences, 66, 1-19(1977).

The compositions include compositions suitable for oral, rectal, ophthalmic, pulmonary, nasal, dermal, topical or parenteral (including subcutaneous, intramuscular and intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

For treating pulmonary conditions such as asthma, the mode of administration may be, for example, oral, parenteral, by inhalation or by suppository. Suitable oral dosage forms are tablets, elixirs, emulsions, solutions, and capsules, including delayed or sustained-release capsules. Parenteral dosage forms include solutions and emulsions. Dosage forms for administration by inhalation include sprays and aerosols. These inhalation fomulations may be administered in metered dosages ranging from 0.1  $\mu$  to 200  $\mu$ g, administered as needed.

For treating allergies or allergic reactions, such as allergic conjunctivitis and allergic rhinitis, the Formula 1 compound may be administered by any conventional mode, e.g. orally, parenterally, topically, sub-

cutaneously or by inhalation.

The oral and parenteral dosage forms are the same type as for the pulmonary treatment. The topical application dosage forms include ointments, salves, controlled-release patches, emulsions, solutions, thixotropic formulations, powders and sprays. For topical application, the percent by weight of the active ingredient (Formula I compound) may vary from about 0.001 to about 10%.

For treating inflammation the mode of administration may be oral, parenteral or by suppository. The various dosage forms are the same as those described above.

For treating skin diseases such as psoriasis, atopic dermatitis and the like, oral, topical or parenteral administration is useful. For topical application to the diseased area, salves, patches, controlled-release patches and emulsions are convenient dosage forms.

For use as an analgesic, i.e. for treating pain, any suitable mode of administration may be used, e.g., oral, parenteral, by insufflation, or by suppository.

For treating cardiovascular conditions such as angina pectoris, any suitable mode of administration, e.g. oral, parenteral, topical, or by insufflation, and dosage form e.g. pills, liquid formulations, controlled-release capsules, and controlled-release skin patches may be used.

In addition to the common dosage forms set out above, the compound of Formula I may also be administered for the various utilities and indications or for inhibiting leukotriene synthesis by controlled-release means and/or delivery devices such as those described in US Patent Specifications US-A-3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719. Dosage forms for application to treat the eye are also disclosed in US-A-4,348,398.

For intravenous administration, a suitable dosage range for anti-asthmatic, anti-inflammatory or anti-allergic use is from 0.01 mg to 20 mg (preferably from 0.1 mg to 10 mg) of a compound of Formula I per kg of body weight per day and for cytoprotective use from 0.002 mg to 100 mg (preferably from 0.02 mg to 30 mg and especially from 0.1 mg to 10 mg) of a compound of Formula I per kg of body weight per day. In the case of an oral composition, a suitable dosage range for anti-asthmatic, anti-inflammatory or anti-allergic use is, e.g. from 1 to 100 mg of a compounds of Formula I per kg of body weight per day, preferably from 5 mg to 40 mg per kg and for cytoprotective use from 0.01 mg to 100 mg (preferably from 0.1 mg to 30 mg and especially from 0.1 mg to 10 mg) of a compound of Formula I per kg of body weight per day.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer. The preferred composition for inhalation is a powder which may be formulated as a cartridge from which the powder composition may be inhaled with the aid of a suitable device. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount.

In practical use, leukotriene inhibitors of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or intravenous. In preparing the compositions for oral dosage form, any of the usual pharmaceutical media are suitable, for example, water, glycols, oils, alcohols, flavouring agents, preservatives, and colouring agents in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders and disintegrating agents in the case of oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which the pharmaceutical carriers are obviously solid. If desired, tablets may be sugar-coated or enteric-coated by standard techniques.

Pharmaceutical compositions of the present invention suitable for oral administration and by inhalation in the case of asthma therapy may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from 25 mg to 500 mg of the active ingredient

and each cachet or capsule contains from 25 to 500 mg of the active ingredient.

The following are examples of representative pharmaceutical dosage forms for the leukotriene inhibitors of Formula I:

5	Injectable Suspension	mg/ml				
	Compound of Formula I	2				
10	Methylcellulose	5.0				
	Tween 80	0.5				
	Benzyl alcohol	9.0				
15	Methyl paraben	1.8				
	Propyl paraben	0.2				
	Water for injection to a	total volume of 1 ml				

20	Tablet	mg/tablet
	Compound of Formula I	25.0
	Microcrystalline Cellulose	325.0
25	Providone	14.0
	Microcrystalline Cellulose	90.0
	Pregelatinized Starch	43.5
	Magnesium Stearate	2.5
30		500
	Capsule la	mg/capsule
35	Compound of Formula I	25
	Lactose Powder	573.5
	Magnesium Stearate	1.5

In addition to the compounds of Formula I, the pharmaceutical compositions of the present invention can also contain other active ingredients, such as cyclooxygenase inhibitors, non-steroidal anti-inflammatory drugs- (NSAIDs), peripheral analgesic agents such as zomepirac diflunisal and the like. The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is combined with an NSAID the weight ratio of the compound of the Formula I to the NSAID will generally range from 1000:1 to 1:1000, preferably 200:1 to 1:200. Combinations of a compound of the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

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NSAIDs can be characterized into five groups:

- (1) the propionic acid derivatives;
- (2) the acetic acid derivatives;
- (3) the fenamic acid derivatives;
- (4) the biphenylcarboxylic acid derivatives; and
- (5) the oxicams

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or a pharmaceutically acceptable salt thereof.

The propionic acid derivatives which may be used comprise: ibuprofen, ibuprufen aluminum, indoprofen, ketoprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen and bucloxic acid. Structurally related propionic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be included in this group.

Thus, "propionic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free -CH(CH<sub>3</sub>)COOH or -CH<sub>2</sub>CH<sub>2</sub>COOH group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g., -CH(CH<sub>3</sub>)COO<sup>-</sup>Na<sup>\*</sup> or -CH<sub>2</sub>CH<sub>2</sub>COO<sup>-</sup>Na<sup>\*</sup>), typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system.

The acetic acid derivatives which may be used comprise: indomethacin, which is a preferred NSAID, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, aiclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, and fenclozic acid. Structually related acetic acid derivatives having similar analgesic and anti inflammatory properties are also intended to be encompassed by this group.

Thus, "acetic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free -CH<sub>2</sub>COOH group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g. -CH<sub>2</sub>COO-Na<sup>\*</sup>), typically attached directly to a ring system, preferably to an aromatic or heteroaromatic ring system.

The fenamic acid derivatives which may be used comprise: mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid and tolfenamic acid. Structurally related fenamic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "fenamic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal antiinflammatory drugs which contain the basic structure:

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which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., -COO<sup>-</sup>Na<sup>+</sup>.

The biphenylcarboxylic acid derivatives which can be used comprise: diffunisal and flufenisal. Structurally related biphenylcarboxylic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "biphenylcarboxylic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:

which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., -COO-Na<sup>+</sup>.

The oxicams which can be used in the present invention comprise: piroxicam, sudoxicam, isoxicam and 4-hydroxyl-1,2-benzothiazine 1,1-dioxide 4-(N-phenyl)-carboxamide. Structurally related oxicams having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "oxicams" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which have the general formula:

wherein R is an aryl or heteroaryl ring system.

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The following NSAIDs may also be used: acemetacin, alminoprofen, amfenac sodium, aminoprofen, anitrazafen, antrafenine, auranofin, bendazac lysinate, benzydamine, beprozin, broperamole, bufezolac, carprofen, cinmetacin, ciproquazone, clidanac, cloximate, dazidamine, deboxamet, delmetacin, detomidine, dexindoprofen, diacerein, di-fisalamine, difenpyramide, emorfazone, enfenamic acid, enolicam, epirizole, etersalate, etodolac, etofenamate, fanetizole mesylate, fenclofenac, fenclorac, fendosal, fenflumizole, fentiazac, feprazone, floctafenine, flunixin, flunoxaprofen, fluproquazone, fopirtoline, fosfosal, furcioprofen, furofenac, glucametacin, guaimesal, ibuproxam, isofezolac, isonixim, isoprofen, isoxepac, isoxicam, lefetamine HCI, leflunomide, lofemizole, lonazolac calcium, lotifazole, loxoprofen, lysin clonixinate, meclofenamate sodium, meseclazone, miroprofen, nabumetone, nictindole, nimesulide, orpanoxin, oxametacin, oxapadol, oxprozin, perisoxal citrate, pimeprofen, pimetacin, piproxen, pirazolac, pirfenidone, pirprofen, pranoprofen, proglumetacin maleate, proquazone, pyridoxiprofen, sudoxicam, suprofen, talmetacin, talniflumate, tenoxicam, thiazolinobutazone, thielavin B, tiaprofenic acid, tiaramide HCI, tiflamizole, timegadine, tioxaprofen, tolfenamic acid, tolpadol, tryptamid, ufenamate, and zidometacin.

The following NSAIDS, designated by company code number, may also be used: 480156S, AA 861, AD1590, AFP802, AFP860, A177B, AP504, AU8001, BPPC, Bu540C, CHINOIN 127, CN100, EB382, EL508, F1044, GV3658, ITF182, KCNTEI6090, LA2851, MR714, MR897, MY309, ONO3144, PR823, PV102, PV108, R830, RS2131, SCR152, SH440, SIR 133, SPAS510, SQ27239, ST281, SY6001, TA60, TVX2706, TVX2706, U60257, and WY41770.

The chemical names of these compounds are, respectively,

2-[4-(2-thiazolyloxy)-phenyl]-propionic acid

2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl-1,4-benzoquinone)

2-(8-methyl-10,11-dihydro-11-oxodibenz[b,f]oxepin-2-yl)propionic acid

3,4,5-trimethoxybenzoyl-ibuprofen

quaiphenesin ibuprofenate

[6-[[1-(3,4-dihydro-8-hydroxy-1-oxo-1H-2-benzopyran-3-yl)-3-methylbutyl]amino]-5-dihydroxy-6-oxo-3-

hexanamido]ammonium chloride chlorhexidine dinaproxenate

4' -acetamidophenyl-2-(5'-p-toluyl-1'-methyl-pyrrole)-acetate

(±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid tromethamine salt

3-methylamino-1-[3-(trifluoromethyl)-phenyl]-2-pyrazoline

Chinoin-127, a rimazolium analogue

45 2-(p-methylallylaminophenyl)propionic acid

 $(\pm)-\alpha$ -[[(2-hydroxy-1,1-dimethylethyl)amino-]methyl]benzyl alcohol

5-[5-(4-chlorophenyl)-2-furanyl]-dihydro-2(3H)-furanone diflunisal lysine salt

3,5-di-t-butyl-4-hydrobenzylidene-y-butyrolactone imidazole 2-hydroxybenzoate

methyl 5,6-E-5,6-methanoeicosa-7E,9E,11Z,14E-eicosatetranoate

50 2,4-diamino-7-methyl-pyrazolo(1,5- $\alpha$ )-1,3,5-triazine

2-(2',4'-difluoro-4-biphenyl)oxypropionic acid

3-methyl-3-(4-acetylaminophenoxy)-2,4-dioxobenzocyclo-1-esanone

4-(p-chlorophenyl)-1-(p-fluorophenyl)pyrazole-3-acetic acid

2-aminomethyl-4-t-butyl-6-propionylphenol hydrochloride glycolic acid {o-(2,6-dichloroanilino)phenyl] ace-

tate ester the 3-hydroxyphthalide ester of (±)-1-(p-cholrobenzoyl)-5-methoxy-2-methylindole-3-acetic acid the phthalidyl ester of diclofenac

2,6-di-t-butyl-4-(2'-thenoyl)phenol 2-[4-(2-oxocyclohexylidenemethyl)phenyl]propionic acid

2-(4-biphenylyl)-4-hexenoic acid

11 $\beta$ ,17,21-trihydroxy- $6\alpha$ -methylpregna-1,4-diene-3,20-dione 21-acetate 17-propionate

4-(2-bromo-4,5-dimethoxyphenyl)-octahydro-2H-quinolizin-2-one

N-(2-pyridyl)-2-methyl-4-cinnamoyloxy-2H-1,2,-benzothiazine-3-carboxamide-1, 1-dioxide

 $17\alpha$ -ethylthio- $9\alpha$ -fluoro- $11\beta$ -hydroxy- $17\beta$ -methylthio-androsta-1,4-diene-3-one 1,1,3-trimethyl-5-phenylbiuret

1-(4-chlorbenzoyl-5-methoxy-2-methyl-1H-indole-3-acetic acid butanediol ester

2-(4-(3-methyl-2-butenyl)phenyl)propionic acid

3-ethyl-1-(3-nitrophenyi)-2,4-[1H,3H]-quinazolindione

6.9-de-epoxy-6,9-(phenylimino)-delta(6,8)-PGI1

1- benzoyl-5-methoxy-2-methylindole-3-acetic acid

(5H-dibenzo[a,d]cyclohepten-5-ylidene)acetic acid.

Finally, NSAIDs which may also be used include the salicylates, specifically aspirin, and the phenyl-butazones, and pharmaceutically acceptable salts thereof.

Pharmaceutical compositions comprising the Formula I compounds may also contain other inhibitors of the biosynthesis of the leukotrienes such as are disclosed in European Patent Specification EP-A-013848I, -0115394, -0136893, -0140709.

The compounds of the Formula I may also be used in combination with leukotriene antagonists such as those disclosed in EP-A-0106585 and -0104885, and others such as those disclosed in EP-A-0056172 and 0061800; and in United Kingdom Specification GB-A-2,058,785.

Pharmaceutical compositions comprising the Formula I compounds may also contain as the second active ingredient, antihistaminic agents such as benadryl, dramamine, histadyl and phenergan. Alternatively, they may include prostaglandin antagonists such as those disclosed in European Patent Specification EP-A-0011067 or thromboxane antagonists such as those disclosed in US Patent Specification US-A-4,237,160. They may also contain histidine decarboxyase inhibitors such as β-fluoromethylhistidine, described in US-A-4,325,961. The compounds of the Formula I may also be advantageously combined with an H<sub>1</sub> or H<sub>2</sub>-receptor antagonist, such as for instance cimetidine, ranitidine, terfenadine, famotidine, and aminothiadiazoles disclosed in EP-A-0040496 and like compounds, such as those disclosed in US Patent Specification US-A-4,283,408; 4,362,736 and 4,394,508. The pharmaceutical compositions may also contain a K\*/H\* ATPase inhibitor such as omeprazole, disclosed in US Patent Specification US-A-4,255,431.

Another embodiment of the present invention comprises the novel compounds encompassed by Formula I and compounds that are their pharmaceutically acceptable salts. These novel compounds are indicated in Table IV.

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TABLE IV

## NOVEL COMPOUNDS OF FORMULA I

R<sup>4</sup> R<sup>2</sup>

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20	Compound	χ	<u> </u>	<u>R</u> 2_	R <sup>3</sup> _	<u>R</u> 4_	<u>R</u> 5_	Ī
20	1	s	н	4-C1	н	н	н	3-OH
	2	S	н	4-C1	Н	н	н	3-OAc
25	31	S	He	4-C1	H	н	н	3-OMe
	4	S	Ac	4-C1	H	Н	н	3OMe
	5	s	н	4-C1	H	H	н	3-08z
30	6	s	н	4-C1	н	н	н :	3-000CH (Me) 2
30	7	s	Me	4C1	н	н		3-000CH(Me) 2
	81	S	Ac	4C1	н	H	н	3-0Ac
	9 <sup>1</sup>	5	Ac	4-C1	н	н	н	3 <b>-</b> 0H
35	10	50 <sub>2</sub>	Me	4-C1	н	н	H	3-0Me
	11	so	He	4-C1	Н	н	н	3-OMe
	12	S	Me	н	7-Ac	н	H	3OMe
40	13	0	He	4-C1	H	н	H	3-0Ac

45

The symbol 1 next to the number of a novel compound indicates which compounds are preferred and the symbol 2 next to the number of a novel compound indicates which compounds are also more preferred.

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5	Compound	X	<u>R</u> 1_	<u>R</u> 2_	<u>R</u> 3_	<u>R</u> 4	<u>8</u> 5_	Ī
	14	S	Me	4-C1	Н	H	H	3-0Ac
10	15	s	Me	Н	н	7-F	н	3-OMe
, 0	16	S	Ac	H	Н	1 <b>-</b> F	н	3OMe
	17	S	Ac	Н	H	1 <b>-</b> F	H	3-0H
15	19	5	Me	н	Н	7-He	H	3-0Me
	20	\$	Н	н	H	7 <b>-</b> F	H	3-0Ac
	21	S	He	н	H	9-C1	Н	3-0Me
20	22	S	Me	H	н	9-C1	н	3-0Ac
	23	5	Me	H	н	7- <del>He</del>	н	3-0Ac
	24	Ş	H	н	Н	9-C1	H	3-0Ac
25	25	\$	H	н	4-CF <sub>3</sub>	H	Н	3-0Ac
	26	\$	H	H	4-C1	H	H	3-0Ts
	27	S	Ac	н	4-C1	7 <b>-</b> F	н	3-OMe
	28	s	Ac	Н	4-C1	7 <b>-</b> F	Н	3-0H
30	29	S	He	н	4-C1	7 <b>-</b> F	н	3-OMe
-	30	s	н	н	2-0Et	4-C1	н	3-OH
	31	SO	Н	Н	H	н	H	3-0Ac
35	32	so <sub>2</sub>	. н	н	H	Н	Н	3-0Ac
	33	so <sub>2</sub>	H	н	4-C1	н	Н	3-OAc
	34 <sup>1</sup>	so,	н	н	4-C1	Н	н	3-OH
40								
	36	so <sub>2</sub>	н	Н	н	7 <b>-</b> F	Н	3-0Ac
	37	so <sub>2</sub>	н	H	4-C1	H	Н	3 <b>-</b> 07s
4P	38	50 <sub>2</sub>		H	4-OH	H	H	3-0H
45	39	s		1-0Me	2-Offe	4-He	н	3-OH
	40	s	н	1OMe	2-OMe	4He	Н	3-0Ac
	41 <sup>1</sup>	50 <sub>2</sub>	H	1-Offe	2-0Me	4-He	H	3-0H
50	42	S0_ 2		40Me	Н	н	H	3-OH

5	Compound	X	<u>R</u> 1_	<u>R</u> 2_	g <sup>3</sup> _	<u>R</u> 4_	<u>R</u> 5_	Ī
	43	s	н	1- <b>0</b> H	2-C(Me) <sub>3</sub>	н 4-с	(Me) <sub>3</sub>	н
10	44	so <sub>2</sub>	H	1-C1	H	Н	H	3-OH
	45	so <sub>2</sub>	Ac	1-C1	Н	H	H	3-OH
	46		Ac	1-C1	Н	H	Н	3-0Ac
15	47	s	He	101	н	H	H	3-0Ac
	48	S	He	1-C1	н	Н	H	3-0H
	49	SO	Н	1OMe	2-Offe	4-He	H	3-OH
20	50	SO	H	1-OMe	2-0Me	4He	H	3-0Ac
	51	s0 <sub>2</sub>	Н	1-0Me	2-0He	4-He	Н	3-0Ac
	52 <sup>1</sup>	s -	H	2-0Me	3-0H	4-8r	7-OHe	Н
25	53 <sup>1</sup>	\$	H	2-Offe	3-0H	4-C1	7-Offe	H
	54 <sup>1</sup>	S	Н	2-Offe	3-QAc	4-8r	7-0He	Н
	55	S	Н	2-Offe	3-0Ac	4-C1	7-0He	H
	56	so <sub>2</sub>	Н	2-0Me	3-OH	4-Br	7-0 <b>1</b> e	н
30	57		н	H	3-OH	Н	7 <b>-</b> F	н
	58	so <sub>2</sub>	H	2-OMe	3-0Ac	4-8r	7-OHe	H
	59 <sup>1</sup>	o T	Ac	2-0Me	3-OH	4-8r	7-OMe	Н
35	60 <sup>1</sup>	0	Ac	2-0Me	3-0Ac	4-8r	7-Offe	Н
	61 <sup>1</sup>	0 00	<sub>2</sub> CH(Me)OAc	2-OMe	3-OH	4-8r	7-Offe	H
	62	oω	2CH(Me)QAc	2-0Me	3-0Ac	4-8r	7-OMe	Н
40	63	Ş	_ H	2-OMe	3-OH	48r	7–He	H
	64	\$	Н	2-0 <b>%</b> e	3-0Ac	4-8r	7- <b>He</b>	H
	65	\$	H	2-OHe	3-OH	4-Br	7 <b>-</b> F	H
45	66	S	H	2-0Me	3-0Ac	4-8r	7 <b>-</b> F	H
.•	67	<b>SO</b>	H	2-0Me	3-0Ac	4-8r	7-OMe	H
	68	502	H	2- <b>ONe</b>	3-OH	H	7- <b>OMe</b>	н
	69	50,	H	2 <b>-0He</b>	3-0Ac	Н	7-0Me	Н
50	70 <sup>1,2</sup>	s	Ac	2-0Me	4-8r	7-0He	н	3-0Ac

5	Compound	x	<u>R</u> 1	<u>R</u> 2_	<u>8</u> 3_	R <sup>4</sup> _	<u>R</u> 5_	Ī
	711.2	s	Ac	2-Offe	4-C1	7-0Me	н	3-0Ac
	72	s	Ac	2-0Me	4-F	7OMe	Н	3-QAc
10	73	s	Ac	2-0Me	4-I	7-OMe	Н	3-0Ac
	74	s	Ac	2-Offe	4-CF <sub>3</sub>	7-Offe	Н	3-0Ac
	75	S	Ac	2-0He	4-CH	7-OMe	н	3-QAc
15	76	S	Ac	2-0Et	4-8r	7-0Et	н	3-0Ac
	77	S	Ac	2-0Et	4-C1	7-0Et	н	3-0Ac
	78	\$	Ac	2-Offe	4-8r	7-0Et	Н	3-0Ac
20	79	s	Ac	2OMe	4-C1	7-0Et	Н	3-0Ac
	80	s	Ac	2-0He	4-F	7-0Et	Н	3-0Ac
	81	S	Ac	2-0Et	4-8r	7QMe	H	3-0Ac
25	82	5	Ac	2-0Et	4-C1	70He	Н	3-0Ac
	83	S	Ac	2-0Et	4-F	7-Offe	Н	3-0Ac
	84	5	Ac	2-0Et	4-CF <sub>3</sub>	7-Offe	н	3-0Ac
	85	s	н	2-0Me	4-8r	7-Offe	H	3-OH
30	86	S	н	2-OMe	4-C1	7-0He	н	3-OH
	87 <sup>1</sup>	\$	н	2-0 <b>Me</b>	4-F	7-0Me	н	3-OH
	<b>88</b> 1	s	н	2-0Me	4-CF <sub>3</sub>	7OMe	H	3-OH
35	89	S	н	2-OMe	4-8r	7-0He	H	3-0Ac
	90 <sup>3</sup>	S	н	2-0Me	4-8r	7-Offe	н	3-08z
	91 <sup>1</sup>	S	Н	2-0 <b>%e</b>	4-Br	7-0He	н :	3-0000He <sub>2</sub>
40	92 <sup>1</sup>	S	н	2-0 <b>11e</b>	4-Br	7-0Me 3-00		н
	93 1	S	Ac	2-0 <b>11e</b>	4-8r	7-0Me	H	3-08z
•	94	5	Ac	2-0He	4-Br	7-0He	H	3-OMe
45	95 <sup>1</sup>	S	Ac	2-OMe	4-8r	7-0Me 3-00	н <sub>2</sub> ∞ <sub>2</sub> н	н
¥ <u>-</u>	96 <sup>1</sup>	S	Ac	2-0He	4-C1	7-Offe 3-00		H
	971	S	CH <sub>2</sub> OAc	2-0 <del>11e</del>	4-8r	7-Offe	н	3-OH
•	98 <sup>1</sup>	S	CH <sub>2</sub> OAc	2- <b>Offe</b>	4-C1	7-OMe	H	3-OH
50	99 <sup>1</sup>	S	CH <sub>2</sub> OAc	2-Offe	4-8r	7-CHe	H	3-0Ac

5	Compound	x	<u>R</u> 1_	<u>R</u> 2_	R <sup>3</sup> _	<u>R</u> 4	<u>R</u> 5_	I
	100	s	CH <sub>2</sub> OAc	2-0 <del>1/e</del>	4-8r	7-0He	Н	3-08z
10	101	S	CH <sub>2</sub> OAc	2-0Me	4-Br	7-0He	н	3-ONe
	1023	\$	CH <sub>3</sub>	2-0Me	4-8r	7-0He	H	3-OH
	103	S	CH <sup>3</sup>	2-Offe	4-8r	7-0He	н	3-0Ac
15	104	\$	CH <sub>3</sub>	2-Offe	4-C1	7-0Me	н	3-OH
	105	S	He	2-Offe	4-F	7-0Me	н	3-OH
	106	\$	He	2-0Me	4-CF <sub>3</sub>	7-0Me	, н	3-OH
00	107	S	CH(Me)OAc	2-OMe	4-8r	7-Offe	н	3-OH
20	108	s a	1(Me)OCOC(Me) <sub>3</sub>	2-OHe	4-8r	7-0He	н	3-OH
	109	\$	CH(Ne)OAc	2-0Me	4-C1	7-0He	н	3-OH
	1101	\$	CH(Me)QAc	2-0He	4F	7-0He	H	3-OH
25	1111	S	CH(Me)QAc	2-Offe	4-CF <sub>3</sub>	7-0He	н	3-OH
	112	S	H	2-Offe	_	7-0Me	3-000 <sub>2</sub> Me	н
	113	S	н	2-OMe	4-8r	7-0He	3-000 <sub>2</sub> Et	н
30	114	\$	н	2-0Me	4–8г	7-Offe 3	3-000 <sub>2</sub> 0H(Me)	OAc H
	115	\$	H	2-OMe	4-C1		3-000 <sub>2</sub> 0H(He)	
	116	S	∞ <sub>2</sub> Me	2-OMe	4-Br	7-0He	Н	3-OH
35	117	\$	ΩEt	2-Offe	4-8r	7-0He	н	3-OH
	118 <sup>1,2</sup>	S	co <sup>2</sup> ct (We) OVC	2-OMe	4-Br	70He	Н	3OH
	119 <sup>1,2</sup>	5	CO <sub>2</sub> CH (He) OAc	2-Offe	4-C1	7-0Me	H	3-OH
	120	5	CO_CH(Ne)OAc	2-0Me	4-F	7-0He	н	3-OH
40	1211,2	\$	CO2CH(Me)OAc	2-0He	4-Br	7-Offe	н	3-0Ac
	122	S	CO2CH (Me)OAc	2-0Me	4-Br	7-Offe :	3-000 <sub>2</sub> CH(Me)	OAC H
	123 <sup>1,2</sup>		Ac	2-0fe			_	3-OH
45	124	S	Ac	2-0Me	4-C1	7-OHe	H	3OH
	125	S	Me	2-0Me	4-8r	7-Offe	Н	3-OMe
	126	S	H	2-OMe	4-8r	7-OMe	Н	3-0Me
50	127	S	CH(Me)OAc	4-C1	H	н	н	3-0Ac
	128	so <sub>2</sub>	Ac	4-C1	н	H	н	3-OH

5	Campound	X	Ŗ¹_	R <sup>2</sup> _	Ŗ <sup>3</sup>	<u>R</u> 4_	<u>R</u> 5_	I
	129	so <sub>2</sub>	Ac	4-C1	н	н	н	3-0Ac
10	130	S	Ac	2-0Et	4-C1	H	H	3-OH
	131 <sup>1</sup>	\$	Ac	2-0Et	4-C)	Н	Н	3-QAC
	132	\$	Ac	2-0Me	4-8r	7-OH	H	3-OH
15	133	S	Ac	2-Offe	4-8r	7-0Ac	H	3-OH
70	134	so <sub>2</sub>	Ac	2-OHe	4-8r	7-Offe	H	3-0H
	135	502	Ac	2-0 <b>1</b> 4e	4-8r	7-0Me	Н	3-0Ac
	136 1	SO.	CO2CH(Me)CA	: 2-OMe	4-8r	7-Offe	H	3-OH
20	1371,2	\$	ထိုင္မတ	H	4-8r	7-OMe	2-Offe	3-CH
			Me C(Me	)3				
	138	S	н	2-OMe	<b>4</b> _I	7OMe	н	3-0H
25	139	S	H	2-CMe	4-CH	7-0Me	H	3-OH
	140	S	H	2-0Et	4 <u>-</u> 8r	7-0Et	Н	3- <b>0</b> H
	141	S	н	2-0Et	4-C1	7-0Et	Я	3-CH
30	142	\$	н	2-0Me	4-8r	7-0Et	H	3-CH
	143	\$	H	2-OMe	4-C1	7-0Et	H	3-CH
	144	\$	H	2-0Me	4 <b>-</b> F	1-0Et	H	3-OH
35	145	\$	H	2-0Et	4-8r	7-OMe	H	3-OH
	. 146	S	Н	2-0Et	4-C1	7-OMe	H	3-OH
	147	\$	н	2-0Et	4 <b>-</b> F	7-0Me	Н	3-OH
40	148	\$	H	2-0Et	4-CF,	7-OMe	H	3-OH

Some of the compounds described herein contain one or more centers of asymmetry and may thus give rise to diastereoisomers and optical isomers. The present invention includes such possible diastereoisomers as well as their racemic and resolved optically active forms.

45 Among preferred novel compounds of the present invention are those having the formula:

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in which the substituents are as set forth in the following table:

		<u>81</u>	_R <sup>2</sup>	_R <sup>3</sup>
5		Н	Br	OH
		н	C1	OН
		н	F	ОН
10		н	¢F <sub>3</sub>	OH
		н	8r	0Ac
		н	8r	<b>OCOPh</b>
15				
			2	_3
	_R <sup>1</sup>		<u>R</u> 2	<u>R</u> 3
20	H		Br	000
	H		Br	ОСН
	Ac		Br	OAc
25	Ac		Cl	OAc
	Ac		Br	oco
				A14.

and those having the formula:

5 R<sup>5</sup> OH R<sup>3</sup>

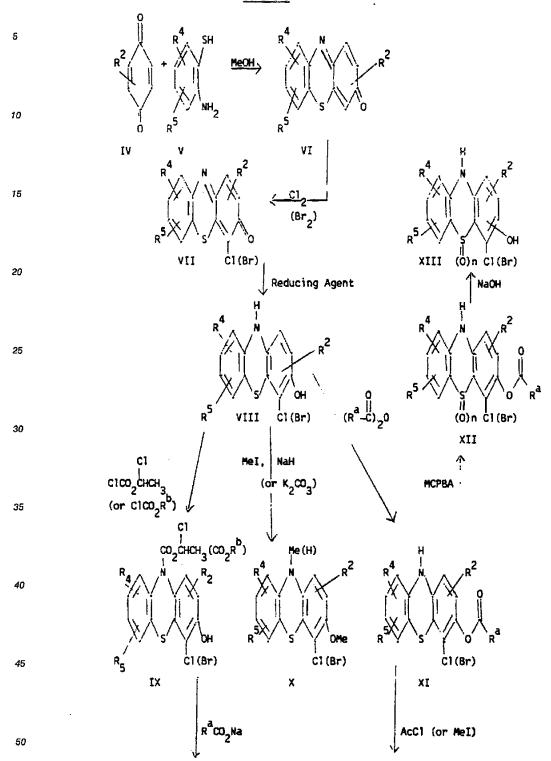
in which the substituents are as set forth in the following table:

20	R <sup>2</sup> _	<u>R</u> 3	R <sup>5</sup>
	Br	OMe	OMe
<b>2</b> 5	C1	. OMe	OMe
	F	OMe	OMe
	I	OMe	OMe
	CF <sub>3</sub>	OMe	OMe
30	CN	OMe	OMe
	Br	OEt	OEt
	Cl	OEt	OEt
35	Br	OMe	OEt
	Cl	OMe	OEt
	F	OMe	<b>OE</b> t
40	Br	OEt	OMe
40	Cl	OEt	OMe
	F	OEt .	OMe
	CF <sub>3</sub>	OEt	OMe
45	3		

as well as the compounds 3-acetoxy-10-acetyl-4-chloro-2,7-dimethoxy-10H-phenothiazine and 3-hydroxy-10-(1-acetoxyethoxycarbonyl)-4-chloro-2,7-dimethoxy-10H-phenothiazine.

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#### SCHEME I (cont'd)

where:

Ra is C1 to C4 alkyl or phenyl.

Rb is C1 to C4 alkyl,

n is 1 or 2.

Reaction of a benzoquinone IV, optimally two equivalents, with 2-aminobenzenethiol V, in a solvent such as acetic acid, acetic acid-water, or a lower alkanol at from -20° to +60°C for 0.25 to 6 hours yields the phenothiazin-3-one VI. Preferably, the solvent is methanol or ethanol, at 0° to 25°C for 0.5 to 2 hours. Halogenation of VI to obtain VII may conveniently be carried out using chlorine or bromine in a lower alkanoic acid such as acetic acid at temperatures of 10° to 50°C. Reduction of VII to VIII is carried out with a reducing agent such as sodium hydrosulfite in a suitable solvent system by stirring at from 10° to 50°C (preferably at room temperature) for 1 to 12 hours (preferably 1 to 4 hours). The solvent system may be a homogeneous one such as dimethylformamide-water or a two-phase system such as ethyl acetate-water or dichloromethane-water.

To prepare a carbamate derivative such as IX, compound VIII is reacted with the appropriate chloroformate reagent in a suitable solvent such as tetrahydrofuran, dioxane or preferably acetonitrile and the mixture heated to reflux for 4 to 24 hours. Reaction of the appropriate chlroalkylcarbamate IX with a metal salt of a carboxylic acid then yields the acyloxyalkoxycarbonyl compound XIV. Preferred salts are those of silver, mercury (II) or sodium, using the corresponding free acid as a solvent, and heating the reaction mixture at 0° to 100° C for from 10 minutes to 2 hours.

To obtain the N,O-dimethylated compounds X, compound VIII is reacted with a methyl halide or a methyl sulfonate (preferably methyl iodide) in the presence of a strong base such as sodium hydride or potassium t-butoxide in a solvent such as tetrahydrofuran or dimethylformamide at 0° to 60°C (preferably room temperature) for from 1 to 24 hours (preferably 1 to 10 hours). The O-methylated compounds X are obtained by substituting a weaker base such as Na<sub>2</sub>CO<sub>3</sub> or K<sub>2</sub>CO<sub>3</sub> for sodium hydride or potassium t-butoxide, and stirring at room temperature for 0.25 hours to 5 hours.

The O-acyl compounds XI are prepared by reacting compound VIII with the desired acid anhydride in pyridine at a temperature of from -25 to +75 °C (preferably 0° to 50 °C) for from 1 hour to 24 hours (preferably 4 to 15 hours). Compound XI is transformed into compound XV by reacting it with an acyl halide (bromide or chloride) in a solvent such as dichloromethane, 1,2-dichloroethane or chloroform (preferably dichloromethane) in the presence of 4 Angstrom molecular sieves for a period of 0.5 to 24 hours (preferably

1 to 6 hours) at a temperature of 0° to 60° (preferably room temperature). Hydrolysis of XV to XVI is carried out by reaction with a base such as LiOH, NaOH or KOH, in mixed solvent such as methanol-water or ethanol-water, at from 0° to 60°C (preferably room temperature) for from 5 minutes to 180 minutes (preferably 10 minutes to 90 minutes). Alternatively, the N-acetyl compound XVI can be prepared from VIII by reacting the latter with an acyl halide, such as acetyl chloride, in a solvent such as dimethyl formamide at from 0° to 50°C (preferably room temperature) for from 0.5 to 4 hours depending on the rate of reaction of the particular components.

The N,O-diacyl compound XV can also be prepared directly from VIII by treating a mixture of VIII and the appropriate acyl halide in a solvent such as dimethylformamide at from 50° to 150°C (preferably 75° to 100°C) for from 2 to 24 hours, preferably from 5 hours to 24 hours to ensure completion of the reaction.

The sulfoxide derivatives XII (n=1) are prepared by treating XI with a peracid such as peracetic acid or meta-chloroperbenzoic acid (MCPBA), in a solvent such as methylene chloride or methylene chloride-methanol for 0.5 to 4 hours at 0° to 30°C. The sulfones XII (n=2) are obtained by reacting XI with a peracid in methylene chloride-methanol, or preferably, 1,2-dichloroethane-ethanol, at the reflux temperature of the mixture for 12 to 24 hours, depending upon the rate of reaction. Hydrolysis of XII to XIII is carried out in a manner similar to that described for the conversion of XV to XVI.

The following examples are provided to illustrate but not limit the invention. Temperatures are in degrees Celsius.

Some of the 3H-phenothiazin-3-one derivatives used as starting materials are described in our European Patent Application EP-A-0 115 394.

### EXAMPLE 1

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#### Synthesis of 3H-phenothiazin-3-one

To a stirring suspension of 1.72 kg (16 mol) of p-benzoquinone in 13 liters MeOH at room temperature was added slowly a solution of 1.0 kg (8 mol) of  $\overline{2}$ -aminothiophenol in 600 ml MeOH over a period of 1 hour. The resulting red mixture was stirred at room temperature for another 2 hours and then the product 3H-phenothiazin-3-one was filtered off. This 3H-phenothiazin-3-one was washed thoroughly with methanol and dried to give 1.07 kg of 3H-phenothiazin-3-one (61.49% yield) , m.p. 157-159 °C.

#### **EXAMPLE 2**

#### Synthesis of 4-chloro-3H-phenothiazin-3-one

To a stirring solution of 500 g (2.34 mol) of 3H-phenothiazin-3-one in 12.5 liters of glacial acetic acid was added 1.25 kg of potassium dichromate. The mixture was stirred at room temperature for 1/2 hour. To this resulting mixture was then added 2.34 mol of a 1M solution of chlorine in glacial acetic acid dropwise over a period of 4 hours. The progress of the reaction was monitored by tlc to ensure no excess chlorine was added. After addition of chlorine was completed the mixture was stirred at room temperature for another 1/2 hour and was then poured into 120 liters of  $H_2O$  with vigorous stirring. The 4-chloro-3H-phenothiazin-3-one which precipitated was allowed to settle overnight. The majority of the aqueous solution was siphoned off and discarded and the rest was filtered. The filtered precipitate was washed thoroughly with water and then rinsed with methanol and was allowed to dry to give 504 g crude 4-chloro-3H-phenothiazin-3-one which was recrystallized from toluene. m.p.: 221  $^{\circ}$  C.

#### **EXAMPLE 3**

### Synthesis of 4-Chloro-3-hydroxy-10H-phenothiazine

A solution of Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> (70 g) in water (500 ml) was added to a solution of 4-chloro-3H-phenothiazin-3-one (50 g) in DMF (1200 ml). The reaction mixture was stirred at room temperature for 3 hours and then poured in 5 liters of water. The resulting precipitate was then filtered to give the 4-chloro-3-hydroxy-10H-phenothiazine (95 %). m.p.: 110°C.

#### **EXAMPLE 4**

### Synthesis of 3-acetoxy-4-chloro-10H-phenothiazine

To a solution of 1.8 g of 4-chloro-3-hydroxy-10H-phenothiazine (see Example 3) in 20 ml of acetic anhydride was added 1.2 ml of pyridine. The reaction mixture was then stirred at ambient temperature for 12 hours and then poured in water (75 ml). The resulting precipitate was filtered, washed with water and dried under vacuum to give 1.65 g of 3-acetoxy-4-chloro-10H-phenothiazine (m.p.: 173 °C).

#### **EXAMPLE 5**

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#### Synthesis of 4-chloro-3-methoxy-10-methyl-10H-phenothiazine

To 25 ml of DMF was added methyl iodide (2.9 ml), 4-chloro-3-hydroxy-10H-phenothiazine (see Example 3) (2.3 g) and sodium hydride (0.672 g). The resulting reaction mixture was stirred at ambient temperature for 12 hours. At 0°C, MeOH was added to destroy the remaining hydride, then H<sub>2</sub>O. The resulting solution was extracted with ethyl acetate and the organic phase, dried and evaporated. The resulting residue was then purified by chromatography on silica gel to give 1.5 g of 4-chloro-3-methoxy-10-methyl-10H-phenothiazine (m.p.: 136°C).

### **EXAMPLE 6**

#### Synthesis 4-chloro-3-methoxy-10-acetyl-10H-phenothiazine

To a solution of 4-chloro-3-acetoxy-10H-phenothiazine (see Example 4) in DMF (10 mls) was added methyl iodide (0.34 ml) and sodium hydride (114 mg). The reaction mixture was stirred at ambient temperature for 12 hours. Methanol and water were then added and the resulting mixture extracted with EtOAc. The organic phases were then collected, dried and evaporated. The resulting residue was purified by chromatography on silica gel (HPLC) to give 0.56 g of 4-chloro-3-methoxy-10-acetyl-10H-phenothiazine (m.p. 136 °C).

#### EXAMPLE 7

#### Synthesis of 3-benzoyloxy-4-chloro-10H-phenothiazine

To a solution of (0.5 g)4-chloro-3-hydroxy-10H-phenothiazine (see Example 3) in pyridine (4 ml) was added 1.2 g of benzoic anhydride. The reaction mixture was stirred at ambient temperature for 7 hours and then poured in  $H_2O$ . The resulting precipitate was then filtered and purified by trituration in CHCl<sub>3</sub>. The resulting solid material was then filtered and dried under vacuum to give 0.6 g of 3-benzoyloxy-4-chloro-10H-phenothiazine (m.p. 203  $^{\circ}$  C).

### **EXAMPLE 8**

#### 40 Synthesis of 4-chloro-3-isobutyryloxy-10H-phenothiazine

To a solution of iso-butyric acid (1.6 ml) in THF (10 ml) at 0  $^{\circ}$  C was added Et<sub>3</sub>N (2.7 ml) and methylchloroformate (1.5 ml). To this resulting suspension was added slowly at 0  $^{\circ}$  C a solution of 4-chloro-3-hydroxy-10H-phenothiazine in THF (10 ml). The reaction mixture was stirred at 5  $^{\circ}$  C for 12 hours, after which H<sub>2</sub>O was added and the resulting aqueous phase extracted with ethyl acetate. The organic layer was then dried and evaporated. The resulting residue was purified by chromatography on silica gel to give 2.25 g of 4-chloro-3-isobutyryloxy-10H-phenothiazine (m.p. 155  $^{\circ}$  C).

#### **EXAMPLE 9**

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#### Synthesis of 4-chloro-3-isobutyryloxy-10-methyl-10H-phenothlazine

To a solution of 4-chloro-3-isobutyryloxy--10H-phenothiazine (see Example 8) (202 mg) in DMF (5 ml) was added methyl iodide (0.2 ml) and sodium hydride (18 mg) at 0° C. The reaction mixture was stirred at ambient temperature for 12 hours. To the reaction mixture was added water and the resulting aqueous layer extracted with EtOAc. The organic layers were collected, dried and evaporated to give a residue which was purified by chromatography on silica gel (plates) to give 100 mg of 4-chloro-3-isobutyryloxy-10-methyl-10H-phenothiazine (m.p. 147° C).

#### **EXAMPLE 10**

### Synthesis of 3-acetoxy-10-acetyl-4-chloro-10H-phenothiazine

To 1.1 g of 3-acetoxy-4-chloro-10H-phenothiazine (see Example 4) was added acetyl chloride (7 ml), DMF (5 ml) and potassium tert-butoxide (0.42 g). The reaction mixture was stirred at ambient temperature for 1 hour and then, poured in water. The resulting precipitate was filtered and purified by chromatography on silica gel to give (1.08 g) 3-acetoxy-10-acetyl-4-chloro-10H-phenothiazine (m.p. 155°C).

#### 10 EXAMPLE 11

### Synthesis of 10-acetyl-4-chloro-3-hydroxy-10H-phenothiazine

To a solution of 4-chloro-3-hydroxyphenothiazine (2.2 g) in DMF (10 ml) was added 10 ml of acetyl chloride. The reaction mixture was stirred at ambient temperature for 1 hour. Ethyl acetate was then added, followed by ice and H<sub>2</sub>O. The organic layer was separated, dried and evaporated. The resulting residue was purified by chromatography on silica gel to give 1.4 g of 10-acetyl-4-chloro-3-hydroxy-10H-phenothiazine (m.p. 214°C).

#### 20 EXAMPLE 12

### Synthesis of 4-chloro-5,5-dioxo-3-methoxy-10-methyl-10H-phenothiazine

To 4-chloro-3-methoxy-10-methyl-10H-phenothiazine (see Example 5) (0.33 g) in acetic acid (10 ml) was added hydrogen peroxide (3 ml). The reaction mixture was stirred at 80 °C for 2 hours. After cooling to ambient temperature, the resulting precipitate was filtered and washed with acetic acid to give the 4-chloro-5,5-dioxo-3-methoxy-10-methyl-10H-phenothiazine (0.2 g) (m.p. 244 °C).

### **EXAMPLE 13**

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# Synthesis of 4-chloro-3-methoxy-10-methyl-5-oxo-10H-phenothiazine

To 4-chloro-3-methoxy-10methyl-10H-phenothiazine (0.5 g) (see Example 5) was added acetic acid (12 ml) and hydrogen peroxide (2 ml). The reaction mixture was heated at 50 °C for 15 minutes and then, evaporated to dryness. The corresponding sulfoxide (0.5 g) (4-chloro-3-methoxy-10-methyl-5-oxo-10H-phenothiazine) was obtained by crystallization (m.p. decomposed at 141 °C).

### EXAMPLE 14

### 40 Synthesis of 2-chloro-3,7-diacetyl-10-methyl-10H-phenothiazine

To 2-chloro-10-methyl-10H-phenothiazine (5 g) in carbon disulfide (100 ml) was added acetyl chloride (2.2 ml) and (portionwise) aluminum chloride (10 g). The reaction mixture was then stirred under reflux for 12 hours. The carbon disulfide was then decanted and the residue treated with ice and concentrated HCI. The resulting precipitate was filtered, washed with water and purified by chromatography on silica gel to yield the title compound, m.p. 185° C.

### EXAMPLE 15

#### Synthesis of 4-chloro-3-methoxy-10-methyl-10H-phenoxazine

This compound was prepared as described in Example 5 following the sequence exemplified in Examples 2 and 3, but starting with 3H-phenoxazine-3-one, instead of 3H-phenothiazine-3-one. The title compound, 4-chloro-3-methoxy-10-methyl-10H-phenoxazine was then obtained (m.p. 107 °C).

#### **EXAMPLE 16**

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### Synthesis of 3,4-dihydroxy-10H-phenothiazine-5,5-dioxide

To a suspension of 4-hydroxy-3H-phenothiazine-3-one-5,5-dioxide (0.8 g) in a mixture of water (20 ml) and ethyl acetate (20 ml) there was added sodium dithionite (2 g) and the resulting mixture was stirred at room temperature for 20 minutes. The insoluble solid was then filtered, washed with water and dried to afford the title compound, m.p. (dec.) 261°C.

<u>Calc'd</u>: C: 54.74; H: 3.45; N: 5.32; S: 12.18 Found: C: 54.85; H: 3.54; N: 5.26; S: 12.11

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#### **EXAMPLE 17**

#### Synthesis of 2,4-di-t-butyl-1-hydroxy-10H-phenothiazine

To a solution of 3,5-di-t-butyl-1,2-benzoquinone (2.2 a) in methanol (15 ml) cooled in an ice bath was added 2-aminothiophenol (1.38 g) and the mixture was stirred for 2 hours. A solid precipitate was filtered off and crystallized from heptane to yield the title compound m.p. 202-212 (dec.). From the methanol filtrate there was obtained, after chromatography and crystallization, an additional crop of the title compound.

#### **EXAMPLE 18**

#### Synthesis of 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine

#### Step 1: Preparation of 2-methoxy-p-benzoquinone

Vanillin (2.432 kg) was added to a solution of sodium hydroxide (640 g) in water (8 1) and cooled to 10 °C with an ice-bath. Then a solution of hydrogen peroxide (30%) (2.4 1) was added at a rate to keep the temperature of the reacting mixture below 30 °C. The addition completed (about 2 hours), the reaction mixture was added over a period of 3 hours to a suspension of sodium periodate (880 g) in water (4 1) and acetic acid (640 ml) cooled with an ice-bath to 10 °C (the temperature of the reacting mixture was kept below 35 °C). The resulting precipitate was filtered, washed with cold water followed by ethanol/hexane (1:1) mixture and air-dried to afford the title compound (1.9 kg), m.p. 144-147 °C.

#### 5 Step 2: Preparation of 2-amino-5-methoxythiophenol

To a stirred solution of 8N potassium hydroxide (1.3 1) was added 2-amino-6-methoxybenzothiazole (750 g) and the mixture was refluxed overnight. The resulting solution was neutralized by the addition of conc. HCl to pH 8.0, then acetic acid to pH 6.0. The precipitate which formed was filtered and washed with water to afford the title compound which was used immediately in Step 3.

#### Step 3: Preparation of 2,7-dimethoxy-3H-phenothiazin-3-one

To a suspension of 2-methoxy-p-benzoquinone (1.15 kg) (Step 1) in methanol (8 1) was added portionwise a suspension of 2-amino-5-methoxythiophenol (from Step 2) in methanol (6 1). The reacting mixture was stirred for 15 minutes, filtered and washed with methanol (8 1). The product isolated was swished with DMF (16 1) for 2 hours, filtered and air-dried. The crude material was dissolved in hot DMF (16 1) (130°-140°C), filtered on Celite and the filtrate cooled to room temperature. The resulting crystals were filtered, washed with methanol (8 1) and air-dried to afford the title compound (70.3 g), m.p. 237-238°C.

#### Step 4: Preparation of 4-bromo-2,7-dimethoxy-3H-phenothiazin-3-one

A solution of bromine (280 g) in acetic acid (2.8 1) was added over a period of 30 minutes to a suspension of 2,7-dimethoxy-3H-phenothiazin-3-one (250 g) (Step 3) in acetic acid (7.5 1) and the mixture was stirred for 2 hours. Methanol (12 1) was added over a period of 30 minutes to the reacting mixture and the black suspension was stirred until it became an orange suspension. Then, the precipitate was filtered, washed with methanol and air-dried to afford the desired compound (312 g), m.p. 260-261 °C.

### Step 5: Preparation of 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothlazine

The compound from Step 4 (300 mg) was suspended in ethyl acetate (100 ml) and a solution of Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> (2 g) in water (40 ml) was then added and the mixture was shaken until the orange-red coloration disappeared. The aqueous layer was decanted, the organic layer was washed with water, dried and evaporated to dryness. The resulting residue was treated with ether and filtered to afford the title compound (240 mg), m.p. 185 °C.

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#### **EXAMPLE 19**

### Synthesis of 3-Acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine

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Using the procedure of Example 4, but substituting 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine for 4-chloro-3-hydroxy-10H-phenothiazine, the title compound was obtained. m.p. 201-203 °C.

#### **EXAMPLE 20**

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#### Synthesis of 3-Acetoxy-2,7-dimethoxy-10H-phenothiazine

Following the procedure of Example 4, but substituting 2,7-dimethoxy-3-hydroxy-10H-phenothiazine for 4-chloro-3-hydroxy-10H-phenothiazine, the title compound was obtained. m.p. 172-174 °C.

#### **EXAMPLE 21**

#### Synthesis of 3-Benzoyloxy-4-bromo-2,7-dimethoxy-10H-phenothiazine

Following the procedure described in Example 7, but substituting 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine for 4-chloro-3-hydroxy-10H-phenothiazine, and heating for 3 hours at 100°C, the title compound was obtained. m.p. 202-203°C.

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#### **EXAMPLE 22**

### Synthesis of 4-Bromo-10-methyl-2,3,7-trimethoxy-10H-phenothiazine

Following the procedure described in Example 5, but substituting 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine for 4-chloro-3-hydroxy-10H-phenothiazine and potassium t-butoxide for sodium hydride, the title compound was obtained, m.p. 143-145 °C.

EXAMPLE 23

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Synthesis of 4-Bromo-2,3,7-trimethoxy-10H-phenothiazine

To a solution of 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine (3.54 g) and methyliodide (2.5 ml) in DMF (20 ml) there was added pulverized potassium carbonate (1.3 g). The reaction mixture was stirred at room temperature. After 15 minutes, another addition of potassium carbonate (1 gram) was made, followed by two other such additions at 15-minute intervals. The final mixture was stirred for a further 15 minutes, then it was diluted with water (100 ml) and ethyl acetate (100 ml). The organic layer was washed twice with water, dried and evaporated down to a solid residue. Crystallization from acetone followed by column chromatography on silica gel eluting with 1:19 ethyl acetate-dichloromethane afforded the pure title compound (1.27 g). m.p. 223-225 °C.

#### 30 EXAMPLE 24

Synthesis of 10-Acetyl-4-Bromo-2,3,7-trimethoxy-10H-phenothiazine

Following the procedure described in Example 6, but substituting 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine for 3-acetoxy-4-chloro-10H-phenothiazine and potassium t-butoxide for sodium hydride, the title compound was obtained. m.p. 147-149 °C.

#### **EXAMPLE 25**

Synthesis of 3-Acetoxy-4-Bromo-2,7-dimethoxy-10-methyl-10H-phenothiazine and 4-bromo-10-methyl-2,3,7-trimethoxy-10H-phenothiazine

To a solution of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine (8.0 g) in N,N-dimethylformamide (80 ml) there was added at room temperature methyl iodide (16 ml) and then potassium t-butoxide (3 g). The mixture was stirred at room temperature. Over a period of 24 hours, seven further additions of methyl iodide (10 ml) and potassium t-butoxide (2 g) were made. The final reaction mixture was diluted With ethyl acetate and the solids filtered. The filtrate was washed three times with brine, dried and evaporated. Flash chromatography of the residue on a column of silica gel, eluting with a 1:9 mixture of ethyl acetate and hexane afforded 3-acetoxy-4-bromo-2,7-dimethoxy-10-methyl-10H-phenothiazine (830 mg, m.p. 189-190 °C) and 4-bromo-10-methyl-2,3,7-trimethoxy-10H-phenothiazine (2.86 g, m.p. 135-137 °C).

#### **EXAMPLE 26**

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Synthesis of 4-bromo-2,7-dimethoxy-3-hydroxy-10-methyl-10H-phenothiazine

To a suspension of 3-acetoxy-4-bromo-2,7-dimethoxy-10-methyl-10H-phenothiazine (0.5 g) in methanol (300 ml) there was added 2N aqueous sodium hydroxide (300 ml) and the mixture was stirred at room temperature overnight. The heterogenous mixture was then acidified with 1N aqueous HCl solution, and

after stirring for 15 minutes the product filtered. This crude product was purified by flash chromatography on a column of silica gel, eluting with a 1:1 mixture of ethyl acetate and hexane, and the pure title product (211 mg) was obtained. m.p. 154-155° C.

#### 5 EXAMPLE 27

### Synthesis of 3-acetoxy-10-acetyl-4-bromo-2,7-dimethoxy-10H-phenothiazine

Method A: To a solution of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine (8.0 g) in 1,2-dichloroethane (300 ml) there was added acetyl bromide (1.79 ml) and powdered 4 Angstrom molecular sieves
(20 g). The resulting mixture was stirred at room temperature for 2 hours, then filtered. The filtrate was
evaporated and the residue co-evaporated with acetone twice. It was then crystallized from
dichloromethane-hexane to afford the pure title compound (7.0 g). m.p.: 185-187° C.

Method B: To a solution of 3-hydroxy-4-bromo-2,7-dimethoxy-10H-phenothiazine (180 g) in dimethylformamide (1.2 L) was added acetyl chloride (230 mL) and the resulting solution was heated at 85 °C for 18 hours. The excess of acetyl chloride was removed under vacuum and the remaining solution was poured slowly onto an ice-water mixture (1:1) (4L) with good mechanical stirring. The resulting precipitate was filtered, dissolved in dichloromethane, dried over sodium sulfate and concentrated under vacuum. The oily residue was dissolved in ether and left to crystallize overnight. The crystals were filtered to afford the title compound (186 g). A sample (10 g) was recrystallized from ethyl acetate to afford the pure product (7 g).

#### **EXAMPLE 28**

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### Synthesis of 10-acetyl-4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine

A mixture of 10-acetyl-3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine (2.0 g) in methanol (40 ml) and 1N aqueous sodium hydroxide solution (40 ml) was stirred at room temperature for 5 hours. The mixture was then made slightly acidic with 1N aqueous HCl and after 15 minutes the crude product was filtered. Crystallization from ethyl acetate afforded the pure title compound (600 mg), m.p.: dec 235 °C.

#### **EXAMPLE 29**

# Synthesis of 10(1-acetoxyethoxycarbonyl)-4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine

#### s Step 1: Preparation of α-chloroethylchloroformate

To a mixture of ethyl chloroformate (108.5 g) and sulfuryl chloride (138 g), benzoyl peroxide (1 g) was added and the mixture was refluxed for 20 hours. The reaction mixture was distilled and the liquid boiling above  $110^{\circ}$  was collected. This was then fractionated using a 30 cm column packed with glass helices to give 32 g of pure  $\alpha$ -chloroethyl chloroformate (b.p.  $118-119^{\circ}$ ).

# Step 2: Preparation of 4-bromo-10-(1-chloroethoxy-carbonyl) -2,7-dimethoxy-3-hydroxy-10H-phenothiazine

A mixture of 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine (5 g)  $\alpha$ -chloroethyl chloroformate (7 g) in THF (50 ml) was refluxed for 18 hours. The mixture was then concentrated to a small volume and flash-chromatographed on a column of silica gel to afford the desired product as a solid which was used directly in the next step.

# Step 3: 10(1-acetoxyethoxycarbonyl)-4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine

A mixture of 4-bromo-10-(1-chloroethoxy-carbonyl) -2,7-dimethoxy-3-hydroxy-10H-phenothiazine (1g) and mercuric acetate (1.46g) in glacial acetic acid (30 mi) was stirred and heated at 85° for 10 minutes. After cooling the mixture was diluted with ethyl acetate, washed with water, aqueous NaHCO<sub>3</sub> solution, and brine, dried and evaporated. Flash chromatography on a column of silica gel, eluting with a 1:3 mixture of ethyl acetate and hexane, afforded the pure title product (599 mg) m.p.: 162-164° C.

#### **EXAMPLE 30**

### Synthesis of 3-acetoxy-10-(1-acetoxyethoxycarbonyl)-4-bromo-2,7-dimethoxy-10H-phenothiazine

By following the procedures described in steps 2 and 3 of example 29, substituting 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine for the 3-hydroxy analog, the title compound was obtained. m.p.: 134-135°C.

#### **EXAMPLE 31**

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#### Synthesis of 3-acetoxy-4-bromo-2-methoxy-7-methyl-10H-phenothiazine

Following the procedure described in Example 3, but substituting 4-bromo-2-methoxy-7-methyl-3H-phenothiazin-3-one for 4-chloro-3H-phenothiazin-3-one, there was obtained the intermediate 4-bromo-3-hydroxy-2-methoxy-7-methyl-10H-phenothiazine, which when used as starting material in the procedure described in Example 4 afforded the title compound. m.p.: 193-194 °C.

#### EXAMPLE 32

#### Synthesis of 3-acetoxy-4-bromo-7-fluoro-2-methoxy-10H-phenothiazine

Following the procedure described in example 31, but substituting 4-bromo-7-fluoro-2-methoxy-3H-phenothiazin-3-one for the 7-methyl analog, there was obtained the intermediate 4-bromo-7-fluoro-3-hydroxy-2-methoxy-10H-phenothiazine, which was used as starting material in the procedure described in Example 4 to afford the title compound. m.p.: 224-226 °C.

#### 25 EXAMPLE 33

#### Synthesis of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine-5-oxide

To a solution of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine (10.0 g) in dichloromethane (125 ml) and methanol (125 ml) there was added at room temperature 85% m-chloro peroxybenzoic acid (4.36 g). The mixture was stirred for one hour and the solid was filtered and washed with ether. This crude product was stirred at room temperature in dichloromethane (50 ml) overnight and filtered again to afford pure title product (7.7g). m.p.: 243-247 °C (dec).

#### 55 EXAMPLE 34

### Synthesis of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide

To a solution of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine (20.0 g) in dichloromethane (250 ml) and methanol (250 ml) there was added 85% m-chloroperoxy benzoic acid (26.0 g) and the resulting mixture stirred at reflux temperature for 18 hours. After cooling, the insoluble solid was collected by filtration. It was suspended in 1,2-dichloroethane (250 ml) and ethanol (250 ml) and there was again added 85% m-chloroperoxybenzoic acid (1.35g). The mixture was refluxed for 18 hours, cooled and filtered to afford the title product (13.0g).

45 m.p.: 258-260°C.

```
<u>Calc'd.</u> C: 44.87; H: 3.29; N: 3.27; S: 7.49
Found C: 44.82; H: 3.21; N: 3.18; S: 7.67
```

#### **EXAMPLE 35**

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#### 5 Synthesis of 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothlazine-5,5-dioxide

To a suspension of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide (10.0 g) in methanol (105 ml) there was added 2N aqueous sodium hydroxide solution (74 ml) and the resulting mixture was

stirred at room temperature for 20 minutes. There was then added 10% aqueous acetic acid solution (250 ml) and a thick precipitate was formed. The mixture was diluted with water (105 ml) and filtered, the solid washed with water and ether, and dried in a desiccator, affording the title compound (9.6 g). Further purification of a small sample was achieved through chromatography on a short column of silica gel, eluting with acetone. m.p.: 252-260° (dec).

#### **EXAMPLE 36**

#### Synthesis of 3-acetoxy-2,7-dimethoxy-10H-phenothiazine-5-oxide

The procedure of Example 33 was employed, substituting 3-acetoxy-2,7-dimethoxy-10H-phenothiazine for the 4-bromo analog, to afford the title compound. m.p.: 238° C (dec).

### 15 EXAMPLE 37

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#### Synthesis of 3-acetoxy-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide

Following the procedure described in Example 34, but substituting 3-acetoxy-2,7-dimethoxy-10H-phenothiazine for the 4-bromo analog, there was obtained the title compound. m.p.: 265-268°C.

#### **EXAMPLE 38**

#### Synthesis of 2,7-dimethoxy-3-hydroxy-10H-phenothiazine-5,5-dioxide

Using the procedure described in example 35, but substituting 3-acetoxy-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide for the 4-bromo analog, there was obtained the title compound. m.p.: 276-278 °C (dec).

Following the procedures described above, the following compounds were prepared:

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$$R^{4}$$

$$\begin{bmatrix} X \\ X \\ N \\ R^{1} \end{bmatrix}$$

39 S Me Cl OAC H 132 40 S Me H OME 7-F 104 20 41 S AC H OME 7-F 192 42 S AC H OH 7-F 195 43 S AC H OAC 7-F 144-145 25 44 S Me H OAC 7-F 175-176 46 S Me H OAC 7-F 175-176 46 S Me H OAC 9-Cl 59 47 S Me H OAC 9-Cl 87-88 30 48 S Me H OAC 9-Cl 117 50 S H H OAC 9-Cl 117 50 S H CF3 OAC H 133 35 51 S H Cl OTS H 178 52 S AC Cl OME 7-F 206 53 S AC Cl OME 7-F 209 40 54 S Me Cl OME 7-F 122 55 SO H H OAC H 220	Example		_		_		
39 S Me Cl OAC H 132 40 S Me H OME 7-F 104 20 41 S AC H OME 7-F 192 42 S AC H OAC 7-F 195 43 S AC H OAC 7-F 144-145 25 44 S ME H OAC 7-F 175-176 46 S ME H OAC 7-F 175-176 46 S ME H OAC 7-F 175-176 47 S ME H OAC 9-Cl 87-88 30 48 S ME H OAC 9-Cl 117 50 S H H OAC 9-Cl 117 50 S H CF3 OAC H 133 35 51 S H Cl OTS H 178 52 S AC Cl OME 7-F 206 53 S AC Cl OME 7-F 209 40 54 S ME Cl OME 7-F 209 55 SO H H OAC H 220	No.	Х	_R <sup>1</sup>	_R <sup>2</sup>	R <sup>3</sup>	_R <sup>4</sup>	m.p. (°C)
20 41 S Me H OME 7-F 104 20 41 S Ac H OME 7-F 92 42 S Ac H OH 7-F 195 43 S Ac H OAC 7-F 144-145 25 44 S Me H OAC 7-F 175-176 46 S Me H OAC 7-F 175-176 46 S Me H OAC 9-C1 59 47 S Me H OAC 9-C1 87-88 30 48 S Me H OAC 9-C1 117 50 S H H OAC 9-C1 117 50 S H CF <sub>3</sub> OAC H 133 35 51 S H C1 OTS H 178 52 S AC C1 OME 7-F 206 53 S AC C1 OME 7-F 209 40 54 S Me C1 OME 7-F 122 55 SO H H OAC H 254-256					- "		
20 41 S Ac H OMe 7-F 92 42 S Ac H OH 7-F 195 43 S Ac H OAC 7-F 144-145 25 44 S Me H OME 7-Me 102 45 S H H OAC 7-F 175-176 46 S Me H OME 9-C1 59 47 S Me H OAC 9-C1 87-88 30 48 S Me H OAC 7-Me 108-110 49 S H H OAC 9-C1 117 50 S H CF <sub>3</sub> OAC H 133 35 51 S H C1 OTS H 178 52 S AC C1 OME 7-F 206 53 S AC C1 OME 7-F 209 40 54 S Me C1 OME 7-F 122 55 SO H H OAC H 254-256	39	s	Me	Cl	OAc	Н	132
42 S Ac H OH 7-F 195 43 S Ac H OAC 7-F 144-148 25 44 S Me H OME 7-Me 102 45 S H H OME 9-C1 59 46 S Me H OAC 9-C1 87-88 30 48 S Me H OAC 7-Me 108-110 49 S H H OAC 9-C1 117 50 S H CF <sub>3</sub> OAC H 133 35 51 S H C1 OTS H 178 52 S AC C1 OME 7-F 206 53 S AC C1 OME 7-F 209 40 54 S Me C1 OME 7-F 122 55 SO H H OAC H 254-256	40	S	Me	Н	OMe	7-F	104
43 S Ac H OAC 7-F 144-145 44 S Me H OME 7-ME 102 45 S H H OAC 7-F 175-176 46 S ME H OME 9-C1 59 47 S ME H OAC 9-C1 87-88 30 48 S ME H OAC 7-ME 108-110 49 S H H OAC 9-C1 117 50 S H CF <sub>3</sub> OAC H 133 35 51 S H C1 OTS H 178 52 S AC C1 OME 7-F 206 53 S AC C1 OME 7-F 209 40 54 S ME C1 OME 7-F 122 55 SO H H OAC H 254-256	41	S	Ac	H	OMe	7-F	92
25 44 S Me H OMe 7-Me 102 45 S H H OAC 7-F 175-176 46 S Me H OAC 9-C1 59 47 S Me H OAC 9-C1 87-88 30 48 S Me H OAC 7-Me 108-110 49 S H H OAC 9-C1 117 50 S H CF <sub>3</sub> OAC H 133 35 51 S H Cl OTS H 178 52 S AC Cl OME 7-F 206 53 S AC Cl OME 7-F 209 40 54 S Me Cl OME 7-F 122 55 SO H H OAC H 254-256	42	S	Ac	H	OH	7-F	195
45 S H H OAC 7-F 175-176 46 S Me H OME 9-C1 59 47 S Me H OAC 9-C1 87-88 30 48 S Me H OAC 7-Me 108-110 49 S H H OAC 9-C1 117 50 S H CF <sub>3</sub> OAC H 133 35 51 S H C1 OTS H 178 52 S AC C1 OME 7-F 206 53 S AC C1 OM 7-F 209 40 54 S Me C1 OME 7-F 122 55 SO H H OAC H 220 56 SO <sub>2</sub> H H OAC H 254-256	43	S	Ac	H	OAc	7-F	144-145
46 S Me H OME 9-C1 59 47 S Me H OAC 9-C1 87-88 48 S Me H OAC 7-Me 108-110 49 S H H OAC 9-C1 117 50 S H CF <sub>3</sub> OAC H 133 35 51 S H C1 OTS H 178 52 S AC C1 OME 7-F 206 53 S AC C1 OM 7-F 209 40 54 S Me C1 OME 7-F 122 55 SO H H OAC H 254-256	44	S	Me	H	OMe	7-Me	102
30 48 S Me H OAC 9-C1 87-88 48 S Me H OAC 7-Me 108-110 49 S H H OAC 9-C1 117 50 S H CF <sub>3</sub> OAC H 133 35 51 S H C1 OTS H 178 52 S AC C1 OME 7-F 206 53 S AC C1 OM 7-F 209 40 54 S Me C1 OME 7-F 122 55 SO H H OAC H 254-256	45	S	H	H	OAc	7-F	175-176
30 48 S Me H OAC 7-Me 108-110 49 S H H OAC 9-C1 117 50 S H CF <sub>3</sub> OAC H 133 35 51 S H C1 OTS H 178 52 S AC C1 OME 7-F 206 53 S AC C1 OM 7-F 209 54 S Me C1 OME 7-F 122 55 SO H H OAC H 254-256 56 SO <sub>2</sub> H H OAC H 254-256	46	s	Me	H	OMe	9-Cl	59
48 S Me H OAC 7-Me 108-110 49 S H H OAC 9-C1 117 50 S H CF <sub>3</sub> OAC H 133 35 51 S H Cl OTS H 178 52 S AC Cl OME 7-F 206 53 S AC Cl OH 7-F 209 40 54 S Me Cl OME 7-F 122 55 SO H H OAC H 254-256	47	S	Me	H	OAc	9-C1	87-88
50 S H CF <sub>3</sub> OAc H 133  51 S H Cl OTS H 178  52 S Ac Cl OMe 7-F 206  53 S Ac Cl OH 7-F 209  54 S Me Cl OMe 7-F 122  55 SO H H OAC H 220  56 SO <sub>2</sub> H H OAC H 254-256	48	S	Me	H	OAc	7-Me	108-110
35	49	S	H	H	OAc	9-Cl	117
35	50	S	H	CF <sub>3</sub>	OAc	H	133
53 S Ac Cl OH 7-F 209 54 S Me Cl OMe 7-F 122 55 SO H H OAC H 220 56 SO <sub>2</sub> H H OAC H 254-256	51	S	н	-	OTs	H	178
54 S Me CI OME 7-F 122 55 SO H H OAC H 220 56 SO <sub>2</sub> H H OAC H 254-256	52	S	Ac	Cl	OMe	7-F	206
55 SO H H OAC H 220 56 SO <sub>2</sub> H H OAC H 254-256	53	S	Ac	Cl	OH	7-F	209
56 SO <sub>2</sub> H H OAC H 254-256	5 4	S	Me	CI	OMe	7-F	122
56 SO <sub>2</sub> H H OAC H 254-256 57 SO <sub>2</sub> H Cl OAC H 274-277	55	so	H	H	OAc	H	220
57 SO <sub>2</sub> H Cl OAc H 274-277	56	so <sub>2</sub>	H	Н	OAc	H	254-256
	57	so <sub>2</sub>	H	Cl	OAc	H	274-277
<sup>45</sup> 58 SO <sub>2</sub> H Cl OH H 286	58	so <sub>2</sub>	Н	Cl	OH	Н	286
59 SO <sub>2</sub> н н он 7-г >220	59	so <sub>2</sub>	H	Н	OH	7-F	>220
60 SO <sub>2</sub> H H OAc 7-F 222	60	so <sub>2</sub>	H	H	OAc	7-F	222

	Example		_	_	_		
	No.	Х	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	m.p. (°C)
5	61	so <sub>2</sub>	H	Cl	OTs	Н	>240
	62	so <sub>2</sub>	H	ОН	OH	H	261
	63	so <sub>2</sub>	H	OMe	OH	н	279
10		2					

#### **EXAMPLE 64**

### Synthesis of 4-chloro-2-ethoxy-3-hydroxy-10H-phenothlazine

By following the procedure described in Step 5 of Example 18, but substituting 4-chloro-2-ethoxy-3H-phenothiazin-3-one for 4-bromo-2,7-dimethoxy-3H-phenothiazin-3-one, the title compound was obtained, m.p. 186-189 °C.

### **EXAMPLE 65**

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# Synthesis of 1,2-dimethoxy-3-hydroxy-4-methyl-10H-phenothiazine, 5,5-dioxide

Starting with 1,2-dimethoxy-4-methyl-3H-phenothiazin-3-one, and using the procedures described in Step 5 of Example 18, Example 19, Example 34 and Example 26, the title compound was obtained, m.p. 218-220°C.

### **EXAMPLE 66**

# Synthesis of 4-Bromo-2,7-dimethoxy-3-hydroxy-10-(1-pivaloyloxyethoxycarbonyl)-10H-phenothiazine

Following the procedure of Example 29, Step 3, but substituting sodium pivaloate in place of mercuric acetate and pivalic acid in place of acetic acid, and heating at 85° for 4 hours, the title compound was obtained, m.p. 85°.

#### Claims

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1. A pharmaceutical composition capable of inhibiting leukotriene biosynthesis or action in mammals and containing a pharmaceutical diluent, carrier or excipient and a compound of Formula I:

$$\begin{array}{c|c}
R^4 \\
X \\
N \\
R^5
\end{array}$$

$$\begin{array}{c}
X \\
N \\
R^1
\end{array}$$

$$\begin{array}{c}
R^2 \\
R^3
\end{array}$$

in which

X is Se, S, SO, SO<sub>2</sub> or O;

 $R^1$  is H;  $C_{1-6}$  alkyl; acetyl;  $(C_{1-6}$  acyloxy)- $(C_{1-5}$  alkyl); benzoyl; substituted benzoyl having  $C_{1-3}$  alkyl, halogen, CN, CF<sub>3</sub>, COOR<sup>6</sup>, CH<sub>2</sub>COOR<sup>6</sup>, (CH<sub>2</sub>)<sub>n</sub>NR<sup>8</sup>R<sup>9</sup> (where n is 0, 1 or 2),  $C_{1-3}$  alkoxy, and/or OH substitution, (herein called "substituted as herein defined"); carbamoyl; CO-NHR<sup>7</sup>; COOR<sup>7</sup>; p-toluenesulfonyl; methanesulfonyl; an acyl group such that  $R^1$ -OH is an essential amino acid; benzyl;

phenethyl;  $(CH_2)_pOR^a$  where  $R^a$  is  $C_{1-6}$  alkyl or phenyl and p is an integer from 1 to 5 when  $R^a$  is phenyl and is an integer from 1 to 6 when  $R^a$  is alkyl;  $(CH_2)_nCOOR^6$  where n is 0, 1 or 2; or  $(C_{1-6}$  acyloxy)- $(C_{1-6}$  alkoxy) carbonyl;

each of  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$ , independently of the others, is hydrogen;  $C_{1-6}$  alkyl;  $C_{2-6}$  alkenyl or -(CH<sub>2</sub>)- $_{q}$ M where q is 0 or an integer from 1 to 6 and M is (a) -OR<sup>16</sup>; (b) halogen; (c) -CF<sub>3</sub>; (d) -SR<sup>16</sup>; (e) phenyl or substituted phenyl as herein defined; (f) COOR<sup>6</sup>; (g) -CO-R<sup>14</sup>; (h) tetrazolyl; (i) -NH-CO-R<sup>7</sup>; (j) -NR<sup>8</sup>R<sup>9</sup>; (k) -NHSO<sub>2</sub>R<sup>10</sup> where R<sup>10</sup> is OH,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy or phenyl; (l) -CO-CH<sub>2</sub>OH; (m) -SOR<sup>11</sup> where R<sup>11</sup> is  $C_{1-6}$  alkyl, phenyl, substituted phenyl as herein defined, (CH<sub>2</sub>)<sub>m</sub>COOR<sup>6</sup> where m is an integer from 1 to 6, CN, formyl, or  $C_{1-4}$  perfluoroalkyl; (n) -CONR<sup>8</sup>R<sup>9</sup>; (o) -SO<sub>2</sub>NR<sup>8</sup>R<sup>9</sup>; (p) -SO<sub>2</sub>R<sup>13</sup> where R<sup>13</sup> is hydrogen, OH,  $C_{1-5}$  alkyl, phenyl, substituted phenyl as herein defined, (CH<sub>2</sub>)- $_{m}$ COOR<sup>6</sup> where m is as defined above, CN, formyl, or  $C_{1-4}$  perfluoroalkyl; (q) -NO<sub>2</sub>; (r) -O-CO-R<sup>14</sup>; (s) O-CO-NR<sup>8</sup>R<sup>9</sup>; or (t) -CN;

each  $R^6$ , independently of the others, is hydrogen,  $C_{1-6}$  alkyl or phenyl;

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each  $R^7$ , independently of the others, is  $C_{1-6}$  alkyl, benzyl, phenyl or  $(C_{1-6}$  acyloxy)- $(C_{1-6}$  alkyl);

each R<sup>8</sup> and each R<sup>9</sup>, independently of any others, is hydrogen, C<sub>1-4</sub> acyl, phenyl, or substituted phenyl as herein defined; or an R<sup>8</sup> and an R<sup>9</sup> are joined through the N to which they are both attached to form a heterocycloalkyl group having from 5 to 8 ring atoms;

each R<sup>14</sup>, independently of the others, is hydrogen,  $(CH_2)_rCOOR^6$  where r is 0 or an integer from 1 to 4;  $C_{1-6}$  alkoxy;  $(C_{1-6}$  alkoxy;  $(C_{1-6}$  alkoxy); phenyl; substituted phenyl as herein defined; or  $C_{1-6}$  aminoalkyl such that R<sup>14</sup>COOH is an essential amino acid;

each  $R^{16}$ , independently of any others, is hydrogen,  $(C_{1-5} \text{ alkoxy})$ - $(C_{1-5} \text{ alkyl})$ ,  $C_{1-6} \text{ alkyl}$ ; benzyl;  $(C_{1-6} \text{ acyloxy})$ - $(C_{1-6} \text{ alkyl})$ ; phenyl; substituted phenyl as herein defined;  $-CH_2$ )<sub>m</sub>COOR<sup>6</sup> where m is as defined above; CN; formyl; perfluoroalkyl; or  $CH_2$ - $R^{12}$  where  $R^{12}$  is  $C_{1-5}$  alkyl, dimethylamino or phenyl; and T is hydrogen or  $-OR_{15}$ , where  $R_{15}$  is hydrogen,  $C_{1-6}$  alkyl,  $(C_{1-6} \text{ alkyl})$ -acyl, phenylacyl, substituted phenyl-acyl as herein defined; benzoyl; substituted benzoyl as herein defined; or arylsulfonyl; and compounds that are pharmaceutically acceptable salts thereof.

- 2. A composition as claimed in Claim 1 in which, in the formula, X<sub>1</sub> is S, SO, SO<sub>2</sub> or O and the other substituents are as defined in Claim 1.
- 3. A composition as claimed in Claim 2 in which  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are all other than  $C_{2-6}$  alkenyl.
- 4. A composition as claimed in Claim 3 in which, in the formula, X is S or O; R¹ is H; C₁-6 alkyl; C₁-6 acyl; (C₁-6 acyloxy)-(C₁-6 alkyl); (C₁-6 alkoxy)-(C₁-6 alkyl); benzoyl; benzoyl substituted as herein defined; carbamoyl; CO-NHR²; COOR²; (CH₂)pOR² where R² is C₁-6 alkyl or phenyl, and p is an integer from 1 to 5; (CH₂)nCOOR⁵ where n is 0, 1 or 2; or (C₁-6 acyloxy)-(C₁-6 alkoxy) carbonyl;

M, if included in  $R^2$ ,  $R^3$ ,  $R^4$  or  $R^5$  is (a)  $-OR^{16}$ ; (b) halogen; (c)  $-CF_3$ ; (d)  $-SR^{15}$ ; (e)  $COOR^6$ ; (f)  $-NH-CO-R^7$ ; (g)  $-NR^8R^9$ ; (h)  $-SOR^{11}$  where  $R^{11}$  is  $C_{1-6}$  alkyl or  $C_{1-4}$  perfluoroalkyl; (i)  $-SO_2R^{13}$  where  $R^{13}$  is  $C_{1-6}$  alkyl or  $C_{1-4}$  perfluoroalkyl; (j)  $-O-CO-R^{14}$  where  $R_{14}$  is H,  $C_{1-6}$  alkyl, phenyl or substituted phenyl as herein defined; (k)  $O-CO-NR^8R^9$ ; or (1) -CN;

each  $R^{16}$ , independently of the others, is hydrogen;  $C_{1-6}$  alkyl; benzyl;  $(C_{1-6}$  acyloxy)- $(C_{1-6}$  alkyl) or  $C_{1-4}$  perfluoroalkyl;

T is hydrogen or  $-OR_{15}$ , where  $R_{15}$  is hydrogen,  $C_{1-6}$  alkyl,  $(C_{1-6}$  alkyl)-acyl, phenylacyl, substituted phenyl-acyl as herein defined, benzoyl or substituted benzoyl as herein defined; and the other variables are as defined in Claim 3.

- 5. A composition as claimed in Claim 1 in which, in the formula X is O or S.
- R¹ is hydrogen, C₁-4 alkyl, C₁-4 alkylacyl, (CH₂)<sub>p</sub>OR² where R² is C₁-4 alkyl or phenyl and p is 1, 2 or 3, (C₁-4 acyloxy)-(C₁-4 alkyl), (C₁-4 alkoxy)carbonyl or (C₁-4 acyloxy)-(C₁-4 alkoxy)carbonyl; each of R², R³, R⁴ and R⁵, independently of the others, is hydrogen, halogen, hydroxyl; C₁-3 alkyl; C₁-3 alkylthio; C₁-5 acyloxy; benzoyloxy; C₁-3 trihaloalkyl; C₁-4 aminoalkyl; C₁-5 acyl; (CH₂)<sub>m</sub>COOR⁵, where m is 0, 1, 2, 3 or 4 and R⁵ is H, phenyl or C₁-5 alkyl; or (C₁-4 acyloxy)-(C₁-4 alkoxy)carbonyl; and T is as defined in Claim 1.
  - 6. A composition as claimed in Claim 1 in which the compounds of Formula i are represented by Formula III:

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in which

 $R^1 \text{ is H, } C_{1-4} \text{ acyl., } (C_{1-4} \text{ acyloxy})\text{-}(C_{1-4} \text{ alkyl}), \text{ or } C_{1-4} \text{ acyloxy})(C_{1-4} \text{ alkoxy})\text{carbonyl};$ 

R<sup>2</sup> is halogen;

R3 is OH, C1-5 acyloxy, benzoyloxy, or (C1-4 acyloxy)-(C1-4 alkoxy)carbonyloxy;

 $R^4$  is H, OH,  $C_{1-4}$  alkoxy or  $C_{1-4}$  acyloxy and is located at either position 1 or position 2;

 $R^5$  is OH,  $C_{1-4}$  alkoxy or  $C_{1-4}$  acyloxy;

T is hydrogen or  $C_{1-4}$  alkoxy; or are pharmaceutically acceptable salts of such compounds.

20 7. A composition as claimed in Claim 1 in which, in the formula, the variables are as set forth in the following table:

	Compound	x	<u>R</u> 1	2	R <sup>3</sup>	4 R	<u>R</u> 5	Ť
25								
	1	5	н	Н	H	H	н	H
	2	S	Me	2-t-8u	1-1-Bu	H	н	1-OH
30	3	s	Me	2-t-8u	4-t-Bu	н	Н	1-0Me
	4	S	Me	2-t-8u	4-t-8u	н	н	1-OAc
	5	s	Ac	2-t-Bu	4-t-8u	H	Н	1-0H
35	6	S	н	2-t-8u	1-L-Bu	H	н	1-OMe
	7	s	н	2-t-Bu	4-t-8u	H	н	1-0Ac
	8	0	н	2-t-Bu	4-t-8u	H	Н	1- <b>OH</b>
	9	S	CH <sub>2</sub> OAc	2-t-8u	4-t-8u	H	н	1-OH
40	10	s	н	1-C1	H	Н	H	3-OH
	11	S	н	1-C1	<b>31</b>	H	11	3-0Ac
	12	s	н	1- <b>C1</b>	н	11	H	3-0Me
45	13	s	Me	1-01	н	Н	н	3-OH
	14	S	Нe	1-C1	н	H	Н	3-0Ac
	15	S	Me	1-C1	Н	н	н	3-OMe
50	16	S	CH <sub>2</sub> OAc	1-01	н	н	H	3-CMe
00	17	\$	CH <sub>2</sub> CAc	1-01	н	H	H	3-OAc
	18	0	H	1-C1	н	11	!;	3-00
	19	0	Me	1-C1	Н	Н	H	3-0H
55	20	0	Ме	1-01	Н	н	н	3-0Ac
	21	0	Не	1-C1	H	H	H	3-0Me

	Compound	X	R 1	<u>R</u> 2	R <sup>3</sup>	<u>R</u> 4	<u>R</u> S	<u> </u>
					•			
5	22	0	Ac	1-01	<b>}</b> 1	Ħ	H	3-0Ac
	23	0	CH <sub>2</sub> OAc	1-¢1	Н	H	H	3-0Me
	24	Se	Me	1-C1	н	Н	н	3-0Me
10	25	so	н	1-C1	11	11	11	3-OH
	26	so	н	1-01	H	11	П	3-0Me
	27	so	н	1-c1	H	11	11	3-OAc
-	28	so	Me	1-C1	н	H	н	3-011
15	29	so	Me	1 C1	н	н	H	3 CAL
	30	SO	Me	1-C1	н	H	H	3-0Me
	31	so <sub>2</sub>	н	1-01	н	н	н	3-OH
20	32	so <sub>2</sub>	Н	1-C1	H	11	П	3-0Ac
	33	so <sub>2</sub>	н	1-C1	н	Н	н	3-0 <b>He</b>
	34	so <sub>2</sub>	He	1-C1	н	Н	н	3-0 <b>Ac</b>
25	35	so <sub>2</sub>	Me	1-C1	7-0CH <sub>2</sub> CO <sub>2</sub> H	H	н	3-0Ac
	36	so <sub>2</sub>	Me	1 C1	н	н	н	3 GHz
	37	so <sub>2</sub>	Ac	1-C1	Н	н	н	3-OH
	38	502	Ac	1-C1	н	н	н	3-0Ac
30	39	so <sub>2</sub>	Ac	1-01	н	H	н	3-0Me
	40	so	Ac	1-C1	н	н	Н	3-011
	41	so	Ac	1-01	н	Н	н	3-OAc
35	42	so	Ac	1 01	н	Н	н	3 -0Mc
	43	502	CH <sub>2</sub> OAc	1-01	н	H	н	3-0H
	44	50 <sub>2</sub>	CH <sub>2</sub> OAc	1-01	н	н	н	3-0Ac
40	45	50 <sub>2</sub>	CH <sub>2</sub> OAc	1-C1	н	H	н	3-CMe
	46	\$	CH <sub>2</sub> Ph	) i	H	11	11	н
	47	S	Me	Н	11	Н	Ш	11

	Campound	x	<u>R</u> 1	_R <sup>2</sup>	<u>8</u> 3 .	_R <sup>4</sup>	<sub>R</sub> 5	Ţ
5	48	5	Ac	н	н	н	н	Н
	49	S	CH <sub>2</sub> CAc	н	н	н	н	н
	50	0	н	Н	H	н	н	н
10	51	0	He	Н	н	H	11	П
	52	0	Ac	Н	Н	H	H	н
	53	Se	н	Н	н	H	H	11
15	54	Se	<del>He</del>	Н	н	Н	H	H
75	55	Se	Ac	Н	н	Н	Н	н
	56	Se	CH <sub>2</sub> OAc,	H	н	Н	Н	н
	57	so	н	Н	H	H	J1	11
20	58	SO	Me	Н	н	Н	Ħ	H
	59	so <sub>2</sub>	Ac	н	н	н	H	н
	60	s	H	H	н	H	Н	3-OH
25	61	S	н	н	н	H	н	3-0Ac
	62	\$	H	Н	Н	H	н	3-0 <b>4</b> e
	63	5	Me	н	Н	Ħ	11	3-0Ac
30	64	s	Me	н	H	11	<b>11</b>	3-OH
30	65	S	Me	н	11	11	11	3-OMe
	66	S	Ac	Н	H	H	11	2-0H
	67	S	Ac	Н	Н	H	Ħ	3-QAc
35	68	S	Ac	Н	н	н	H	30Me
	69	S	CH <sub>2</sub> CAc	H	H	н	Н	3-0H
	70	S	CH <sub>2</sub> OAc CH <sub>2</sub> OAc	H	Ħ	H	н	3-0Ac
40	71	s		Н	H	н	Н	3-0Me
	72	Same as	compounds	s 60-71 i	but X <b>=0</b>			
	73	Same as	compounds	s 60–71	but X=Se			
45	74	S	н	4-C1	н	н	н	3011
<del>-</del> 0	75	S	H	4-c1	Н	н	н	30Me
	76	S	H	4-C1	н	н	H	3OAc

	Compound	x	<u>R</u> 1	R <sup>2</sup>	<u>8</u> 3	R <sup>4</sup>	_R <sup>5</sup>	Ţ
								_
5	17	\$	Me	4-C1	Н	Ħ	H	3-011
	78	\$	Me	4-C1	Н	Н	н .	3-OAC
	79	S	Me	4-C1	Н	Н	H	3-OMe
10	80	S	Ac	4-C1	H	Н	H	3-OH
	81	S	Ac	4-C1	Н	Н	Н	3-0Ac
	82	S	Ac	4-C1	Н	H	Н	3-0Me
	83	S	Me	4-C1	H	Н	H	3-0-8z
15	84	5	Me	4-C1	H	H	н 3-0	COCH (Me) 2
	85	S	Me	4-C1	н	H	H 3-0	COC (Me) 3
	86	<sup>SO</sup> 2	Н	4-C1	Ħ	11	11	3-011
20	87	so <sub>2</sub>	н	4-OH	H	11	ii .	3-0H
	88	202 2	н	4-C1	н	11	11	3-0Ac
	89	so <sub>2</sub>	н	4-C1	н	H	н	3-0He
25	90	so <sub>2</sub>	Me	4-C1	н	н	Н	3-011
	91	so <sub>2</sub>	Нe	4-C1	н	н	н	3-0Ac
	92	so <sub>2</sub>	Me	4-C1	н	H	11	3-0Me
	93	so <sub>2</sub>	Ac	4-C1	н	н	H	3-011
30	94	so <sub>2</sub>	Ac	4-C1	н	н	H	3 -0Ac
	95	so <sub>2</sub>	Ac	4 C1	н	Н	H	3 OML
	96	s	CH <sub>2</sub> OAc	4 C1	н	н	н	11
35	97	S	CH_DAC	4-C1	Н	Н	П	3-011
	98	S	CH <sub>2</sub> OAc	4-C1	н	H	H	3-0/c
	99	S	CH <sub>2</sub> OAc	1-C1	н	Н	н	3-0Me
40	100	so <sub>2</sub>	CH <sub>2</sub> OAc	4C1	Н	Н	н	3 34
	101	502	CH <sub>2</sub> OAc		н	Н	Н	3 -0Ac
	102	so <sub>2</sub>	CH <sub>2</sub> OAc	4-C1	н	H	11	3-CMe
	103	-	compounds	5 74-103	but X-SO			
<b>4</b> 5	104	Same as	compounds	s 74–103	but X <b>=</b> 0			
	105	Same as	compounds	5 74-103	but R <sub>4</sub> i	s 7-Cl		

	Compound	Χ .	<u>R</u> 1	<u>R</u> 2	_ <u>R</u> 3	_R <sup>4</sup>	R <sup>5</sup>	T
5	106	Same as	compound	105 but	X=0			
•	107	Same as	compounds	74-103	but R <sub>4</sub> is	: 7-0Me		
	108	Same as	compound	107 but	X=O			
	109	Same as	compounds	74-103	but R4 is	s 7-(C <sub>1</sub>	-C <sub>6</sub> alky	1)
10	110	Same as	compound	109 but	X=0			
	111	Same as	compounds	74-103	but R <sub>4</sub> is	s 7-(CC	Me)	
	112	Same as	compound	111 but	X=0			
15	113	Same as	compounds	74-103	but R <sub>4</sub> is	s 7-[(C	H <sub>2</sub> ) mCOOF	t], wherein
		m is 0-	4					
	114	Same as	compound	113 but	X=0			
20	115	Same as	compounds	74-103	but R <sub>4</sub> i	s 9-C1		
	116	5	Н	4-Et	н	H	Н	3-OH
	117	S	Me	4-Et	н	Н	н :	3-OCOCH <sub>2</sub> Ph
	118	s	Me	4-Et	н	н	H	3-0Ac
25	119	S	Me	4-Et	н	Н	н	3-OMe
	120	S	Н	4-0Et	н	Н	Н	3-0H
	121	S	н	4-0Et	H	H	H	3-OMe
30	122	S	Me	4-0Et	Н	Н	Н	3-OMe
	123	s	Me	4-0Et	н	н	Н	3-0Ac
	124	S	H	2-0Et	7-0Et	н	н	3-OH
35	125	S	н	2~0Et	7-0Et	H	H	3-OMe
	126	s	Me	2-0Et	7-0Et	н	Н	3-OMe
	127	5	Me	2-0Et	7-0Et	H	Н	3-OAc
	128	S	H	н	H	н	Н	3-0Ac
40	129	s	Me	н	Н	н	3-Ac	н
	130	\$	Ac	н	Н	H	3-Ac	3-0Ac
	131	S	н	7-Ac	H	н	3-Ac	H
45	132	s	Me	7-Ac	Н	н	3-Ac	H
	133	S	Ac	7-Ac	н	H	3-Ac	Н

	Compound	X	R <sup>1</sup>	<u>R</u> 2	_R <sup>3</sup>	4	<u>R</u> 5	T
				•				
5	134	S	CH <sub>2</sub> OAc	7-Ac	Н	н	3-Ac	н
	135	s	н	2-Me	4-C1	H	н	3-OH
	136	S	Me	2-Me	4-C1	н	Н	3-0Ac
10	137	S	н	7-Me	2-Me	H	H	3-0H
	138	S	Me	7-Me	2-Me	H	Ħ	3-0Ac
	139	S	Н	2-0Èt	4-C1	H	H	3-011
	140	s	Me	2-0€t	4-C1	Н	н	30Ac
15	141	s	Н	2-S-n-Bu	4C1	н	н	3-0H
	142	s	He	2-5-n-Bu	4-C1	н	н	3-0Ac
	143	s	He	4-5-n-Bu	н	н	H	3-0Ac
20	144	S	Me	2-0-Me	4-Br	н	Н	3- <b>0</b> Ac
	145	S	Me	2-0-Me	4-C1	н	Н	3-0Ac
	146	s	Me	2-0-Me	4-Br	н	Н	3-00
25	147	S	н	2-0-Me	3OH	H	H	7-0Me
	148	S	Н	1-0Me	3-0H	Н	H	7 -OMe
	149	S	н	2-OMe	3-0H	1-8r	н	7-0Me
	150	S	н	1-0 <b>M</b> e	3-OH	2-Br	н	7-OMe
30	151	S	н	1-0 <b>M</b> e	3-0H	4-8r	H	7 -0Me
	152	s	н	1-0 <b>M</b> e	3-OH	2-01	Н	7-0Me
	153	s	н	1-0 <b>H</b> e	3OH	4-C1	н	7-UMC
35	154	S	н	2-0Me	3-OH	1-C1	H	7-0Me
	155	s	H	2-0 <b>4e</b>	3-OH	4-C1	Н	7 -OMe
	156	S	Н	2-0Et	3-OH	1-Br	н	7-0£t
40	157	\$	Н	2-0Et	3-OH	4-8r	H	7-0Et
	158	S	H	2-0Et	3-0H	1'-01	Н	7-Ott
	159	S	н	2-0£ t	3OH	4-C1	н	7-0E L
	160	5	Н	2-CMe	30H	1-Br	7-0Me	9-CMe
<b>4</b> 5	161	S	н	2-0Me	3-0H	4-8r	7-CMe	8-0 <b>%</b> e

	Compound	x	<u>R</u> 1	<u>R</u> 2	<sub>R</sub> 3	<u>R</u> 4	<u>R</u> 5	Τ
					•			
5	162	S	H	2-0Me	3-OH	4F	н	7-0Me
	163	S	н	2-0 <b>%</b> e	3-OH	4-CF <sub>3</sub>	н	7-OMe
	164	S	H	2-0 <b>He</b>	3-OH	4-8r	Н	7-0Et
10	165	5	H	2-0 <b>1</b> 4e	3-OH	4-C1	Н	7-0£ t
	166	S	H	2-0 <b>Me</b>	3-OH	4_F	Н	7-0Et
	167	S	H	2-0Me	3OH	<b>4</b> –I	Н	7-0Me
15	168	S	н	2-0 <b>%</b> e	3-OH	4-CF <sub>3</sub>	Н	7-0£ t
79	169	S	H	2-0Et	3-OH	4-Br	H	7-0Me
	170	S	Н	2-0E t	3-OH	4-C1	H	7-0Mc
	171	S	н	2-0Et	3-OH	4F	н	7-0Me
20	172	S	н	2-0Et	3- <b>0H</b>	4-CF <sub>3</sub>	н	7-0Me
	173	s	н	1-0He	2-0Me	3-OH	4-8r	
	174	S	н	1~0Me	3-OH	н	Н	2-0Me
25	175	S	н	10Me	3-OH	4-8r	н	2-0Me
	176	Same as	compounds	147-175	but X=0			
	177	Same as	campounds	147-175	but X=SO	2		
30	178	S	н	2-SMe	3-OH	4-8r	н	7-0Me
30	179	s	н	2-OMe	3-OH	4-Br	7-SMe	
	180	so <sub>2</sub>	н	2~\$0 <sub>2</sub> Me	3-0H	4-Br	Н	7-CMe
	181	Same as	compounds	147-175	but X=50			
35	182	S	н	4-C1	Н	H	Н	3-08z
	183	\$	н	4-C1	Н	H	H 3-0	COCH (Me) 2
	184	S	Ac	Н	н	7-F	11	3-0Ac
40	185	\$	Me	Н	Н	7-He	H	3-0Me
	186	S	н	Н	H	7_F	B	3-0Ac
	187	\$	Me	Н	,H	9-C1	H	3-OMe
45	188	\$	Me	н	н	9-C1	н	3-0Ac
<del></del>	189	\$	Me	н	н	7-Me	11	3~0Ac

	Compound	x	<u>R</u> 1	2 <u>R</u> 2	R <sup>3</sup>	R <sup>4</sup>	8 <sup>5</sup>	Ţ
					•			
5	190	S	н	н	H T	9-C1	н	3-0Ac
Ū	191	S	н	н	4-CF <sub>3</sub>	H	11	3 -QAc
	192	S	Н	н	4C1	Н	Н	3-01s
	193	s	Ac	н	4-C1	7 <b>-</b> F	н	3-0Me
10	194	S	Ac	н	4-C1	7-F	H	3-0H
	195	S	Me	Н	4-C1	7-F	H	3-0Me
	196	so	н	н	Н	ii.	Ħ	3 OAL .
15	197	50 <sub>2</sub>	н	н	H	Н	Н	3 CAC
	198	so <sub>2</sub>	н	н	Н	11	11	3 OH
	199	so <sub>2</sub>	Н	н	H	7-F	11	3-0Ac
20	200	s0 <sub>2</sub>	н	н	4-C1	H	Н	3-0Ts
20	201	s	н	1-OMe	2-0Me	4-Me	H	3-OH
	202	S	н	1-OMe	2-0 <b>He</b>	4-Me	н	3-0Ac
	203	so <sub>2</sub>	н	1-0Me	2-0Me	4-Me	H	3-0H
25	204	so <sub>2</sub>	H	40Mc	Ħ	lt	11	3 - O! !
	205	s	н	2-0Me	3-0H	4-Br	7-OMe	Н
	206	S	н	2-OMe	3-0Ac	4–Br	7-0Me	Н
30	207	S	н	2-CHe	3-0Ac	4-C1	7-0Me	Н
	208	so <sub>2</sub>	н	2-CMe	3-OH	4-Br	7-0Me	H
	209	s	н	2-OMe	3-OAc	7-0Me	4-Br	H
35	210	S	н	2-0Me	3-0Ac	7-0Me	4-8r	Н
	211	S	н	2-0Me	3-08z	7-0Me	4-Br	н
	212	5	Me	2-CMe	3-0Me	7-0Me	4–8r	н
	213	S	н	2-OMe	3-OMC	7-CMe	4-8r	Н
40	214	S	Ac	2-OMe	3-0Ac	7-0He	4-Br	н
	215	S	Ac	2-OMe	3-0H	1-0He	4-8r	н
	216	S	Ac	2-OMe	3-CMe	7-C#e	4-8r	н
45	217	S	Me	2-OMe	3-0 <b>Ac</b>	7-CMe	4-Br	н

	Compound	x	<u>R</u> 1 <u>R</u>	2	<u>R</u> 3 F	4	<sub>R</sub> 5	Τ
5	218	S	Me	2-0 <b>Me</b>	3-OH	7OMe	4-8r	Н
	219	<sup>SO</sup> 2	н	2-CMe	3-OH	7~OMe	4-Br	н
	220	50 <sub>2</sub>	н	2-0Me	3OAc	7-0He	4-Br	н
10	221	so <sub>2</sub>	н	2-OMe	3-0Ac	7-0 <b>4</b> e	4-8r	н
	222	SO	н	2-OMe	3-OAc	7-0 <b>Me</b>	4-8r	н
	223	SO	н	2-CMe	3-0Ac	7-0 <b>H</b> e	4-8r	н
	224	S	н	2-CMe	3-000 He	4-Br	7-0Me	н
15	225	S	н	2-OMe	_	4-8r	7-0Me	н
	226	S	н	20 <b>Me</b>	3-000_CH(Me)OAc	4-8r	7-OMe	н
	227	S	н	2-0Me	-		7-04e	н
20	228	S	co₂e	2-OMe	3-он	4-Br	7-0Me	Н
	229	S	ω <sub>z</sub> Et	2OMe	3-OH	4-Br	7-0Me	н
	230	Ş	CD_CH (Me) OAc	2-0 <b>4e</b>	3-OH	4-Br	7-0Me	H
25	231	\$	CO2CH (Me) OAc			4-C1	7-0Me	Н
	232	S	CO_CH(Me)OAc			4_F	7-OMe	Н
	233	S	Ω <sub>2</sub> CH(#e)OAc	2-0Me	3-0Ac	4Br	7-0Me	H
	234	S	-		3-000 <sub>2</sub> CH(Me)0Ac	4-Br	7-0He	н
30	235	0	Ac	2-OMe	3-0H	4-Br	7-0 <b>He</b>	Н
	236	0	Ac .	2-OMe	3-OAc	4-Br	7~0Me	Н
	237	0	CO <sub>2</sub> CH(Me)OAc	2-0Me	3-OH	4-Br	7-0Me	н
35	238	0	CO <sub>2</sub> CH (Me) OAc		3-0Ac	4-Br	7 OMe	н
	239	s	н	2-OMe	3-OH	4-Br	7-Me	H
	240	S	н	2-0Me	3OAc	4-Br	7-Me	н
40	241	s	н	2-OMe	3-OH	4-8r	7-F	н
	242	S	Н	2-0Me	3-0/c	1-8r	7-F	н

	Compound	<u>x</u>	<u>R</u> 1_	E	<u>R</u> 3_	<u>R</u> 4_	<u>R</u> 5_	<u>r</u>
5	243	s	н	н	П	н	H	OCOEt
	244	S	н	2-C1	3-C1	Н	11	000-n-Pr
	245	\$	Н	Н	4-C1	н	н	000-n-8u
10	246	s	Н	1-He	н	н	н	H
.0	247	S	н	2-CF <sub>3</sub>	н	н	Н	H
	248	s	н	2-Et	н	н	Н	11
	249	S	н -	н	3-01	7-OMe	н	Н
15	250	5	н	Н	3-C1	7-C1	Н	Н
	251	s	Н	H	3-NO <sub>2</sub>	Ħ	7-NO <sub>2</sub>	н
	252	s	Н	3-NMe <sub>2</sub>	11	R	7-NMe <sub>2</sub>	н
20	253	S	Н	1-0H	11	!1	11	Н
	254	S	н	3-0Ac	7 -F	11	11	11
	255	S	н	3-CH <sub>2</sub> COMe	4-C1	11	H	H
25	256	s	н	3-0000HHe <sub>2</sub>	н	4-C1	н	н
	257	5	Aç	3-0Me	4-C1	Н	H	н
	258	0	н	2 -CF <sub>3</sub>	н	H	н	<b>#</b> 1
	259	S	Me	н	3-0Me	Н	4-C1	н
30	260	<sup>50</sup> 2	Н	4-C1	3-OH	H	Н	н
	261	s	Нe	7-F	4-C1	3-0 <b>Me</b>	н	н
	262	S	Нe	3-0Me	7-Me	Н	н	н
35	263	S	Ac	4-C1	Н	H	Н	Н
	264	S	Ac	3-OAc	4-C1	н	Н	Н
	26 <b>5</b>	so <sub>2</sub>	Ac	4_C1	н	н	н	3-OH
40	266	50 <sub>2</sub>	Ac	4-C1	н	н	Н	3 OAc
,•	267	50 <sub>2</sub>	Ac	4-8r	н	н	Н	3-0Ac

	Compound	žχ	<u>R</u> 1_	EZ_	R3_	<u>R</u> 4_	<u>R</u> 3_	Ī
5	268	so <sub>2</sub>	∞ <sub>2</sub> CH(Me)0Ac	4-C1	<b>H</b> .	н	н	3-0H
v	269	so <sub>2</sub>	Н	4-C1	н	н 3-00	CD_CH(Me)OAc	н
10	270	0	Ac	4-C1	н	11	H	3-0Ac
	271	0	∞ <sub>2</sub> CH(Me)0Ac	4-C1	н	н	н	3-0H
15	21 <b>2</b>	0	CO_CH(Me)OAc	4-C1	н	Н	H	3 -O/C
						-		
20	273	0	H	4-C1	н	11 3-0	CO <sub>2</sub> CH (Me) OAc	H
	274	\$	CH <sub>2</sub> OAc	4-C1	н	н	н	3-0/c
25	275	S	CH(Me)OAc	4-C1	H	н	н	3-0Ac
30	276	\$	н	2-OMe	3-OH	7-OH	н	#
	277	\$	Н	20Me	3-OH	7-OH	4-Br	н
35	278	s	н	2-0Me	3-OAc	7OH	4-Br.	н
	279	\$	н	2-0 <b>Me</b>	3-0Ac	7-0Ac	: 4-Br	H .

	Compound	<u>x</u>	<u>R</u> 1_	<u>R</u> 2	<u>R</u> 3	<u>R</u> 4	<u>R</u> 5_	Ī
5	280	S	Ac	2 -0Me	3-OH	7-OH	4-Br	н
	281	\$	Ac	2-0Me	3-0Ac	7-OH	4-8r	н
	282	S	Ac	2-0Me	3-OAc	7-0Ac	4-8r	H
	283	5	Ac	2-0Me	3-0H	7-0Ac	4-8r	н
10	284	50 <sub>2</sub>	Ac	2-0Me	3-0H	4-Br	7-OMe	Н
	285	50 <sub>2</sub>	CO <sub>2</sub> CH(Me)OAc	2-OMe	3-0Ac	4-Br	7 - OMe	н
15	286	50 <sub>2</sub>	Ac	2-OMe	H I 3-000 <sub>2</sub> COAc i Me	4-8r	7-0Me	н
20	287	502	Ac	2-OMe	3-0Ac	4-Br	7-0Me	н
25	288	so <sub>2</sub>	CO <sub>2</sub> CH(Me)OAc	2-OMe	3-0H	4-8r	7-0Me	н
	289	S	Ac	2-0Et	3-0Ac	4-C1	н	н
	290	S	Ac	2-0Et	3-OH	4-C1	н	Н
30	291	S	Me	н	7-Ac	н	Н	3-CMe
	292	S	Me	Н	н	7-F	н	3-OMe
	293	s	Ac	н	Н	7-F	Н	3-OMe
35	294	s	Ac	Н	н	7-F	н	3-0H

<sup>8.</sup> A composition as claimed in Claim 7 in which the compound has one of the formulae numbered 13, 14, 31, 37, 38, 73, 76, 78, 79, 80, 81, 82, 84, 86, 87, 88, 92, 93, 94, 124, 139, 147, 151, 153, 155, 157, 159, 162, 163, 164, 165, 169, 170, 178, 179, 182 to 223 inclusive, 225 to 242 inclusive, 260 or 267 to 294 inclusive.

11. Compounds having the formula:

A composition as claimed in Claim 7 in which the compound has one of the formulae numbered 79, 80, 81, 86, 88, 93, 94, 197, 198, 214, 215, 226, 230, 233, 235, 236, 237, 275, 280, 283, 284, 287, 288, 289 and 290.

 <sup>10.</sup> A composition as claimed in Claim 1 for use in (a) inhibiting mammalian leukotriene biosynthesis or action; (b) treating cardiovascular conditions; (c) treating inflammation; (d) treating allergies; (e) treating pain; (f) treating asthma; or (g) treating skin conditions.

$$\begin{array}{c|c}
R^4 & X & R^2 \\
\hline
R^5 & I & R^3 & I
\end{array}$$

in which the substituents are as set forth in the following table:

	Compound	X	<u>R</u> 1_	<u>R</u> 2_	<u>R</u> 3_	<u>R</u> 4_	<u>R</u> 5_	Ī
15	3	s	Me	4-C1	н	н	н	3-OMe
	8	S	Ac	4-C1	н	н	Н	3-0Ac
20	9	s	Ac	4-C1	н	н	н	3-OH
25	Compound	<u>x</u>	<u>R</u> 1_	E2	<u>R</u> 3_	<u>R</u> 4_	<u>R</u> S_	Ī
	27	s	Ac	Н	4-C1	7 <b>-</b> F	н	3-OMe
	28	s	Ac	н	4-C1	7 <b>-</b> F	H	3-OH
30	29	\$	Me	н	4C1	7-F	н	3-0Me
	30	S	н	н	2-0Et	4-C1	н	3-OH
	32	so <sub>2</sub>	н	н	н	н	Н	3-0Ac
35	33	so2	н	н	4 <b>-</b> C1	Н	н	3-0Ac
	34	so2	H	H	4-C1	н	Н	3-OH
	39	5	н	1-0Me	2-0 <b>Me</b>	4-Me	н	3-0H
40	40	\$	Н	1-OMe	2-0Me	4-He	н	3-0Ac
-	41	SO <sub>2</sub>	н	1-OMe	2-0Me	4- <b>H</b> e	Н	3-0H

	Compound	<u>x</u>	<u>R</u> 1_	<u>R</u> 2_	<u>R</u> 3_	<u>R</u> 4_	R <sup>5</sup> _	I
5	43	\$	н	1-OH	2-C(Me) <sub>3</sub>	н 4-4	C(Me) <sub>3</sub>	н
	49	so	н	1-0Me	2-0Me	4-Me	н	3-OH
	50	20	Н	1-CMe	2-OMe	4-Me	н	3-0Ac
	51	so <sub>2</sub>	н	1OMe	2-0Me	4_Me	н	3-0Ac
10	52	s ¯	н	2-0Me	3-OH	4-8r	7-0 <b>M</b> e	H
	53	S	Н	2 <b>-</b> 0 <del>1/e</del>	3-OH	4-C1	7-0Me	H
	54	\$	Н	2-OMe	3-0Ac	4 <u>-</u> 8r	7-OMe	н
15	55	S	н	2-OMe	3-OAc	4-C1	7-OMe	Н
	56	so <sub>2</sub>	н	2-0Me	3-OH	4-8r	7-0Me	Н
	58	502	н	2-0 <b>Me</b>	3-0Ac	4-8r	7-OHe	Н
20	59	0	Ac	2-OMe	3-OH	4-8r	7OMe	Н
	60	0	Ac	2-0Me	3-QAc	4-8r	7-0Me	н
	61	0 co,	CH(Me)QAc	2-OMe	3-0H	4-Br	7-0He	H
25	62	_	CH(Me)OAc			4-8r	7-OMe	н
	63	s	H	2-0Me	3-OH	4-8r	7-Me	H
	64	S	H	2-OMe	3-0Ac	4-8r	7-Me	Н
00	65	S	H	2-0Me	3-OH	4 <u>-</u> 8r	7 <b>_</b> F	Н
30	66	\$	н	2-0Me	3-0Ac	4-8r	1-F	Н
	67	SO	н	2~CMe	3-OAc	4-8r	7-0Me	н
	68	so <sub>2</sub>	н	2-0Me	3-OH	н	7-OMe	н
35	69	so <sub>2</sub>	н	2-OMe	3-0Ac	H	7-OMe	н
	70	s	Ac	2-0Me	4-8r	7-0Me	H	3-OAc

	Compound	x	<u>R</u> 1_	<u>R</u> 2_	<u>8</u>	<u>R</u> 4	<u>8</u> _	I
5	71	S	Ac	2-CMe	4-C1	7-OMe	н	3-0Ac
	12	s	Ac	2-OMe	4-F	7-OMe	Н	3-0Ac
	73	S	Ac	2-OMe	4-I	7-0Me	н	3-0Ac
10	74	s	Ac	2-GMe	4-CF <sub>3</sub>	7-0Me	H	3-0Ac
	15	S	Ac	2 -0Me	-	7-0Me		3-0Ac
	76	s	Ac	2-0Et	4-8r	7-0Et	H	3-0Ac
	77	S	Ac	2-0Et	4-C1	7-0Et	H	3-0Ac
15	78	S	Ac	2 -01 <del>1e</del>	4-8r	7-0Et	н	3-0Ac
	79	S	Ac	2-QMe	4-C1	7-0Et	Н	3-0Ac
	80	S	Ac	2-0Me	4-F	7-0Et	H	3-0Ac
20	81	S	Ac	2-0Et	4-Br	7-0Me	Н	3-0Ac
	82	5	Ac	2-0Et	4-C1	7-OMe	н	3-0Ac
	83	S	Ac	2-0Et	4F	7-0 <b>Me</b>	ห	3-0Ac
25	84	S	Ac	2-0Et	4-CF3	7-0 <b>Me</b>	н	3-0Ac
	85	S	н	2-OMe	4-8r	7-CMe	н	3-0H
	86	S	Н	2-OMe	4-C1	7-0Me	H	3-OH
30	87	S	н	2-OMe	4-F	7-0Me	н	3OH
30	88	s .	н	2-OMe	4-CF <sub>3</sub>	7-OMe	H	3-0H
	89	5	н	2-OMe	4-Br	7-CMe	н	3-0Ac
	90	S	н	2-0Me	4-8r	7OMe	н	3-08z
35	91	S	н	2-OMe	4-Br	7-OMe	Н	3-OCOCHMe <sub>2</sub>
	92	\$	Н	2-0Me	4-8r	7-0Me 3-	OCH <sub>2</sub> CO <sub>2</sub> H	н
	93	s	Ac	2-GMe	4-8r	7-0Me	н	3-08z
40	94	5	Ac	2-CMe	4-8r	7-OMe	н	3-OMe
	95	5	Ac	2-GMe	4-Br	7-0Me 3-	OCH2CO2H	н
	96		Ac	2-CMe		7-0Me 3-	OCH2CO2H	н
45	97	s	CH <sub>2</sub> CAc	2-CMe	4-8r	7 -0Me	н	3 -OH
- <del>-</del>	98	s	CH_OAc	2-OMe	4-C1	7 -CMe	Н	3 -OH
	99	S	CH <sub>2</sub> OAc	2-CMe	4-Br		н	3 <i>-</i> 0Ac

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	Сопроила	X	R1_	<u>R</u> 2_	<u>R</u> 3_	<u>R</u> 4	<u>R</u> 5_	<u>T</u>
5	100	\$	CH <sub>2</sub> OAc	2-0Me	4-Br	7-0Me	н	3-08z
	101	5	-	2-0Me	4-Br	7-0Me	H	3-0Me
	102	S	CH <sub>3</sub>	2OMe	4-8r	7-0Me	н	3-OH
	103	5	_	2-OMe	4-8r	7-0Me	н	3-0Ac
10	104	S	-	2-0Me	4-C1	7-0Me	н	3-OH
	105	s	Me	2-OMe	4-F	7-0Me	н	3-OH
	106	S	Me	2-0Me	4-CF <sub>3</sub>	7-0Me	н	3-OH
15	107	S	CH(Me)OAc	2-OMe	•	7OMe	н	3-OH
	108	S CH(	Me)0000(Me)3	2-OMe	4-8r	7OMe	н	3-0H
	109	S	CH(Me)OAc	2-OMe		7-0Me	H	3-OH
20	110	\$	CH(Me)OAc	2-0Me	4-F	7-0Me	н	3-OH
	111	S	CH(Me)OAc	2-0Me	4-CF <sub>3</sub>	7-OMe	Н	3-OH
	112	s	H	2-OMe	_	7-0Me 3-		н
25	113	5	н	2-OMe	4-8r	7-OMe 3-	000 <sub>2</sub> Et	Н
20	114	\$	н	2-OMe	4-Br	7-0Me 3-00	_	
	115	5	н	2-0Me	4-C1	7OMe 3OC	10 <sub>2</sub> CH(Me)	OAc H
	116	S	CO <sub>2</sub> Me				Н	3-OH
30	117		CO_Et				н	3-0H
	118	s c	CH (Me) OAc	2-OMe	4-Br	7-OMe	н	3-0H
	119	\$ 0	CH(Me)OAc	2-OMe	4-C1	7OMe	н	3-0H
35	120	s c	CH (Me) OAc	2-0Me	4-F	7-0Me	Н	3-0H
	121	\$ 0	CH (Me) OAc	2-0Me	4-Br	7OMe	Н	3-0Ac
	122	5 0	CD_CH(Me)OAc	2-0Me	4-8r	7-0Me 3-00	20 <sub>2</sub> CH(Me)	OAc H
40	123	S	Ac ·	2-0Me	4-Br	7-0Me	н	3-он
	124	5	Ac	2-OMe	4-C1	70Me	н	3-OH
	125	\$	Me	2-OMe	4-8r	7-OMe	н	3-0Me
	126	5	H	2-0Me	4-8r	7-0Me	н	3-OMe
45	127	\$	CH(Me)OAc	4-C1	н	н	Н	3-0Ac
	128	s0 <sub>2</sub>	Ac	4-C1	н	H	H	3-OH
		_						

	Compound	X	<u>R</u> 1_	<u>8</u> 2_	R3	<u>R</u> 4	<u>R</u> 5_	I
5	129	50 <sub>2</sub>	Ac	4-C1	Н	н	н	3-OAc
	130	s	Ac	2-0Et	4-C1	н	н	3-OH
	131	s	Ac	2-0£t	4-C1	н	H	3-0Ac
10	132	s	Ac	2-0Me	4-8r	7- <b>0</b> H	н	3-OH
	133	s	Ac	2-0Me	4-8r	7-QAc	н	3-OH
	134	so <sub>2</sub>	Ac	2-0Me	4-8r	7-0Me	H	3-OH
	135	502	Ac	2-0 <b>Me</b>	4-8r	7~0Me	H	3-0Ac
15	136	SO <sub>2</sub>	CO_CH(Me)OAc	2-0Me	4 <u>-</u> 8r	7-0Me	н	3-OH
	137	s ¯	ထိုင္မမထ	H	4-8r	7-0Me	2-0Me	3-OH
			Me C(Me)	3				
20	138	\$	н	2-0 <b>Me</b>	<b>4-</b> I	7-0Me	Н	3-OH
	139	\$	н	2-0 <b>M</b> e	4-CN	7OMe	H	3-OH
	140	S	н	2-0Et	4-8r	7-0Et	H	3-OH
25	141	5	н	2-0Et	4-C1	7-0Et	H	3-OH
	142	\$	H	2-0Me	4-8r	7-0Et	H	3-OH
	143	5	Н	2-0Me	4-C1	7-0Et	н	3-OH
30	144	S	Н	2-0Me	4_F	7-0Et	н	3-OH
	145	\$	Н	2-0Et	4-8r	7-0Me	н	3-OH
	146	\$	н	2-0Et	4-C1	7-0Me	н	3OH
	147	S	Н	2-0Et	4-F	7-Offe	н	3-OH
35	148	\$	H	2-0Et	4-CF <sub>3</sub>	7-0Me	H	3OH

- 12. The compounds having variables in Formula I as numbered 3, 8, 9, 32, 33, 34, 41, 59, 60, 61, 70, 71, 114, 118, 119, 121, 123 or 127 to 137 inclusive in Claim 11.
  - 13. The compounds having variables in Formula I as numbered 70, 71, 118, 119, 121, 123 or 137 in Claim 11.
  - 14. Compounds according to Claim 11 having the formula:

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in which the substituents are as set forth in the following table:

	<u>_</u> R <sup>1</sup>	R <sup>2</sup>	_R <sup>3</sup>
5	н	Br	OH
	н	Cl	ОН
	н	F	OH
10	н	CF <sub>3</sub>	ОН
	н	Br	OAc
	н	Br	OCOPh

	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
20	H	Br	OCOCHMe <sub>2</sub>
	Н	Br	och <sub>2</sub> co <sub>2</sub> H
	Ac	Br	OAc
	Ac	Cl	OAc
25	Ac	Br	ocoph
	Ac	Br	OMe
	Ac	Br	och <sub>2</sub> co <sub>2</sub> h
30	Ac	Cl	осн <sub>2</sub> со <sub>2</sub> н
	CH <sub>2</sub> OAc	Br	ОН
	CH <sub>2</sub> OAc	Cl	OH
35	CH <sub>2</sub> OAc	Br	OAC
	CH <sub>2</sub> OAc	Br	ocoph
	CH <sub>2</sub> OAc	Br	OMe
40	CH <sub>3</sub>	Br	ОН
40	CH <sub>3</sub>	Br ·	OAc
	CH <sub>3</sub>	Cl	ОН
	CH <sub>3</sub>	F	OH
45	CH <sub>3</sub>	CF <sub>3</sub>	OH
	CH (CH <sub>3</sub> ) OAc	Br	OH
	CH (CH <sub>3</sub> ) OCOC (CH <sub>3</sub> ) 3	Br	OH
50	CH (CH <sub>3</sub> ) OAc	Cl	OH
	CH (CH <sub>3</sub> ) OAc	F	OH
	CH (CH <sub>3</sub> ) OAc	CF <sub>3</sub>	ОН
EE	CO <sub>2</sub> CH (Me) OAc	Br	ОН
55	CO <sub>2</sub> CH (Me) OAc	Br	OAc

15. Compounds according to Claim 11 having the formula:

in which the substituents are as set forth in the following table:

	R <sup>2</sup> _	R <sup>3</sup>	<u>R</u> 5
20		•	
	Br	OMe	OMe
	Cl	OMe	OMe
25	F	OMe	OMe
	I	OMe	OMe
	CF <sub>3</sub>	OMe	OMe
	CN	OMe	OMe
30	Br	OEt	OEŁ
	Cl	OEt	OEt
	Br	OMe	OEt
35	Cl	OMe	OEt
	F	OMe .	OEt
	Br	OEt	OMe
40	Cl	OEt	OMe
	F .	OEt .	OMe
	CF <sub>3</sub>	OEt	OMe

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- **16.** 3-Acetoxy-10-acetyl-4-bromo-2,7-dimethoxy-10H-phenothiazine.
- 17. 10-(1-Acetoxyethoxycarbonyl)-4-bromo-2,7-dimethoxy-3-hydyroxy-10H-phenothiazine.
- 18. 3-Acetoxy-10-acetyl-4-chloro-2,7-dimethoxy-10H-phenothiazine.
- 19. 4-Bromo-2,7-dimethoxy-3-hydroxy-10-(1-pivaloyloxyethoxycarbonyl)-10H-phenothiazine.
- **20.** 3-Hydroxy-10-(1-acetoxyethoxycarbonyl)-4-chloro-2,7-dimethoxy-10H-phenothiazine.
  - 21. 3-Acetoxy-10-(1-acetoxyethoxycarbonyl)-4-bromo-2,7-dimethoxy-10H-phenothiazine.

- 22. 3-Hydroxy-10-acetyl-4-bromo-2,7-dimethoxy-10H-phenothiazine.
- 23. A composition as claimed in any one of Claims 1 to 9 additionally comprising an effective amount of a second active ingredient that is a non-steroidal anti-inflammatory drug; a peripheral analgesic agent; a cyclooxygenase inhibitor; a leukotriene antagonist; a leukotriene inhibitor; an H<sub>2</sub>-receptor antagonist; an antihistaminic agent; a prostaglandin antagonist or a thromboxane antagonist.
- 24. A composition as claimed in Claim 23 in which the weight ratio of the compound of Formula I to the second active ingredient is in the range from 1000:1 to 1:1000.
- 25. A composition as claimed in Claim 24 in which the aid ratio is from 200:1 to 1:200.
- 26. A composition according to any one of Claims 23 to 25 in which the second active ingredient is a non-steroidal anti-inflammatory drug.
- 27. A composition according to Claim 26 in which the non-steroidal anti-inflammatory drug is indomethacin.

### Revendications

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20 1. Composition pharmaceutique capable d'inhiber la biosynthèse ou l'action des leucotriènes chez les mammifères et contenant un diluant, véhicule ou excipient pharmaceutique et un composé de formule générale I :

$$\begin{array}{c|c}
R^4 \\
X \\
X \\
R^2 \\
T \\
R^3
\end{array}$$

dans laquelle

X est Se, S, SO, SO<sub>2</sub> ou O:

R¹ est H; un groupe alkyle en  $C_1$ - $C_6$ ; acétyle; (acyloxy en  $C_1$ - $C_6$ )-(alkyle en  $C_1$ - $C_6$ ); benzoyle; benzoyle substitué comportant une substitution alkyle en  $C_1$ - $C_3$ , halogène, CN, CF<sub>3</sub>, COOR<sup>6</sup>, CH<sub>2</sub>COOR<sup>6</sup>, (CH<sub>2</sub>)- $_n$ NR<sup>8</sup>R<sup>9</sup> (où n est égal à 0, 1 ou 2), alcoxy en C<sub>1</sub>-C<sub>3</sub> et/ou OH (que l'on qualifie ici de "substitué tel que défini ici"); carbamoyle; CO-NHR<sup>7</sup>; COOR<sup>7</sup>; p-toluènesulfonyle; méthanesulfonyle; un groupe acyle tel que R¹-OH soit un acide aminé essentiel; benzyle; phénéthyle; (CH<sub>2</sub>) $_p$ OR<sup>8</sup>, où R³ est un groupe alkyle en C¹-C6 ou phényle et p est un nombre entier de 1 à 5, lorsque R³ est un groupe phényle, et est un nombre entier de 1 à 6, lorsque R³ est un groupe alkyle; (CH<sub>2</sub>) $_n$ COOR<sup>6</sup>, dans lequel n est égal à 0, 1 ou 2; ou (alcylxy en C¹-C6)-(alcoxy en C¹-C6) carbonyle;

chacun des radicaux  $R^2$ ,  $R^3$ ,  $R^4$  et  $R^5$ , indépendamment des autres, est un hydrogène; un groupe alkyle en  $C_1$ - $C_6$ ; alcényle en  $C_2$ - $C_6$  ou -( $CH_2$ ) $_qM$ , où q est nul ou un nombre entier de 1 à 6 et M est (a) - $OR^{16}$ ; (b) un halogène; (c) - $CF_3$ ; (d) - $SR^{16}$ ; (e) un groupe phényle ou phényle substitué tel que défini ici; (f)  $COOR^6$ ; (g) - $CO-R^{14}$ ; (h) un groupe tétrazolyle; (i) - $NH-CO-R^7$ ; (j) - $NR^8R^9$ ; (k) - $NHSO_2R^{10}$ , ou  $R^{10}$  est OH, un groupe alkyle en  $C_1$ - $C_6$ , alcoxy en  $C_1$ - $C_6$  ou phényle; (1) - $CO-CH_2OH$ ; (m) - $SOR^{11}$ , où  $R^{11}$  est un groupe alkyle en  $C_1$ - $C_6$ , phényle, phényle substitué tel que défini ici, ( $CH_2$ ) $_mCOOR^6$ , où m est un nombre entier de 1 à 6, CN, un groupe formyle ou perfluoroalkyle en  $C_1$ - $C_4$ ; (n) - $CONR^8R^9$ ; (o) - $SO_2NR^8R^9$ ; (p) - $SO_2R^{13}$ , où  $R^{13}$  est un hydrogène, OH, un groupe alkyle en  $C_1$ - $C_6$ , phényle, phényle substitué tel que défini ici, ( $CH_2$ ) $_mCOOR^6$ , dans lequel m est tel que défini ci-dessus, CN, formyle ou perfluoroalkyle en  $C_1$ - $C_4$ ; (q) - $NO_2$ ; (r) -O-CO- $R^{14}$ ; (s) O-CO- $NR^8R^9$ ; ou (t) -CN;

chaque  $R^6$ , indépendamment des autres, est un hydrogène, un groupe alkyle en  $C_1$ - $C_6$  ou phényle; chaque  $R^7$ , indépendamment des autres, est un groupe alkyle en  $C_1$ - $C_6$ , benzyle, phényle ou (acyloxy en  $C_1$ - $C_6$ )-(alkyle en  $C_1$ - $C_6$ );

chaque R<sup>8</sup> et chaque R<sup>9</sup>, indépendamment des autres, est un hydrogène, un groupe acyle en C<sub>1</sub>-C<sub>4</sub>, phényle ou phényle substitué tel que défini lci; ou un radical R<sup>8</sup> et un radical R<sup>9</sup> sont liés par

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l'intermédiaire du N auquel ils sont tous deux fixés pour former un groupe hétérocycloalkylique comportant 5 à 8 atomes dans le noyau;

chaque R<sup>14</sup>, indépendamment des autres, est un hydrogène, un groupe (CH<sub>2</sub>),COOR<sup>6</sup>, dans lequel r est nul ou un nombre entier de 1 à 4; un groupe alkyle en C<sub>1</sub>-C<sub>6</sub>; alcoxy en C<sub>1</sub>-C<sub>6</sub>; (acyloxy en C<sub>1</sub>-C<sub>6</sub>)- (alcoxy en C<sub>1</sub>-C<sub>6</sub>); phényle; phényle substitué tel que défini ici; ou aminoalkyle en C<sub>1</sub>-C<sub>6</sub> tel que R<sup>14</sup>COOH soit un acide aminé essentiel;

chaque  $R^{16}$ , indépendamment des autres, est un hydrogène, un groupe (alcoxy en  $C_1$ - $C_5$ )-(alkyle en  $C_1$ - $C_5$ ), alkyle en  $C_1$ - $C_6$ ; benzyle; (acyloxy en  $C_1$ - $C_6$ )-(alkyle en  $C_1$ - $C_6$ ); phényle; phényle substitué tel que défini ici; ( $CH_2$ )<sub>m</sub> $COOR^6$ , où m est tel que défini ci-dessus; CN; formyle; perfluroalkyle; ou  $CH_2$ - $R^{12}$ , dans lequel  $R^{12}$  est un groupe alkyle en  $C_1$ - $C_5$ , diméthylamino ou phényle;

et T est un hydrogène ou un groupe - $OR^{15}$ , dans lequel  $R^{15}$  est un hydrogène, un groupe alkyle en  $C_1$ - $C_6$ , (alkyl en  $C_1$ - $C_6$ )-acyle, phénylacyle, (phényl substitué)-acyle tel que défini ci-dessus; benzoyle; benzoyle substitué tel que défini ci-dessus; ou aryisulfonyle; et les composés qui sont leurs sels pharmaceutiquement acceptables.

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- 2. Composition selon la revendication 1, dans la quelle, dans la formule,  $X_1$  est  $S_1$ ,  $SO_2$  ou  $O_1$  et les autres substituants sont tels que définis dans la revendication 1.
- 3. Composition selon la revendication 2, dans laquelle R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> sont tous différents d'un groupe alcényle en C<sub>2</sub>-C<sub>5</sub>.
  - 4. Composition selon la revendication 3, dans laquelle, dans la formule, X est S ou O; R¹ est H; un groupe alkyle en C₁-C₆; acyle en C₁-C₆; (acyloxy en C₁-C₆)-(alkyle en C₁-C₆); (alcoxy en C₁-C₆)-(alkyle en C₁-C₆); benzoyle; benzoyle substitué tel que défini ici; carbamoyle; CO-NHR²; COOR²; (CH₂)pOR², dans lequel R² est un groupe alkyle en C₁-C₆ ou phényle, et p est un nombre entier de 1 à 5; (CH₂)nCOOR⁶, dans lequel n est égal à 0, 1 ou 2; ou (acyloxy en C₁-C₆)-(alcoxy en C₁-C₆)carbonyle;

M, s'il est inclus dans  $R^2$ ,  $R^3$ ,  $R^4$  ou  $R^5$ , est (a)  $-OR^{16}$ ; (b) un halogène; (c)  $-CF_3$ ; (d)  $-SR^{16}$ ; (e)  $COOR^6$ ; (f)  $-NH-CO-R^7$ ; (g)  $-NR^8R^9$ ; (h)  $-SOR^{11}$ , dans lequel  $R^{11}$  est un groupe alkyle en  $C_1-C_6$  ou perfluoroalkyle en  $C_1-C_6$ ; (i)  $-SO_2R^{13}$ , dans lequel  $R^{13}$  est un groupe alkyle en  $C_1-C_6$  ou perfluoroalkyle en  $C_1-C_6$ ; (i)  $-O-CO-R^{14}$ , dans lequel  $R^{14}$  est H, un groupe alkyle en  $C_1-C_6$ , phényle ou phényle substitué tel que défini ici; (k)  $O-CO-NR^8R^9$ ; ou (1) -CN;

chaque  $R^{16}$ , indépendamment des autres, est un hydrogène; un groupe alkyle en  $C_1$ - $C_6$ ; benzyle; (acyloxy en  $C_1$ - $C_6$ )-(alkyle en  $C_1$ - $C_6$ ) ou perfluoroalkyle en  $C_1$ - $C_4$ ;

T est un hydrogène ou un groupe -OR¹⁵, dans lequel R¹⁵ est un hydrogène, un groupe alkyle en C₁-C₆, (alkyl en C₁-C₆)acyle, phénylacyle, (phényl substitué)-acyle tel que défini ici, benzoyle ou benzoyle substitué tel que défini ici;

et les autres variables sont telles que définies dans la revendication 3.

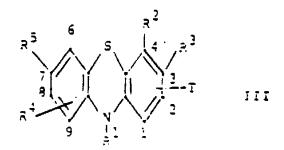
Composition selon la revendication 1, dans laquelle, dans la formule.
 X est O ou S,

R¹ est un hydrogène, un groupe alkyle en  $C_1$ - $C_4$ , alkylacyle en  $C_1$ - $C_4$ , -( $CH_2$ ) $_pOR^a$ , dans lequel R $^a$  est un groupe alkyle en  $C_1$ - $C_4$  ou phényle et p est égal à 1, 2 ou 3, (acyloxy en  $C_1$ - $C_4$ )-(alkyle en  $C_1$ - $C_4$ ), (alcoxy en  $C_1$ - $C_4$ )carbonyle;

chacun des radicaux R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup>, indépendamment des autres, est un hydrogène, un halogène, un hydroxyle; un groupe alkyle en C<sub>1</sub>-C<sub>3</sub>; alcoxy en C<sub>1</sub>-C<sub>3</sub>; alkylthio en C<sub>1</sub>-C<sub>3</sub>; acyloxy en C<sub>1</sub>-C<sub>5</sub>; benzoyloxy; trihalogénoalkyle en C<sub>1</sub>-C<sub>3</sub>; aminoalkyle en C<sub>1</sub>-C<sub>4</sub>; acyle en C<sub>1</sub>-C<sub>5</sub>; (CH<sub>2</sub>)<sub>m</sub>COOR<sup>6</sup>, dans lequel m est égal à 0, 1, 2, 3 ou 4 et R<sup>6</sup> est H, un groupe phényle ou alkyle en C<sub>1</sub>-C<sub>6</sub>; ou un groupe (acyloxy en C<sub>1</sub>-C<sub>4</sub>)-(alcoxy en C<sub>1</sub>-C<sub>4</sub>)carbonyle; et T est tel que défini dans la revendication 1.

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6. Composition selon la revendication 1, dans laquelle les composés de formule I sont représentés par la formule III :



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dans laquelle

 $R^1$  est H, un groupe acyle en  $C_1$ - $C_4$ , (acyloxy en  $C_1$ - $C_4$ )-(alkyle en  $C_1$ - $C_4$ ) ou (acyloxy en  $C_1$ - $C_4$ )-(alcoxy en  $C_1$ - $C_4$ )-carbonyle;

15 R<sup>2</sup> est un halogène;

 $R^3$  est OH, un groupe acyloxy en  $C_1$ - $C_5$ , benzoyloxy ou (acyloxy en  $C_1$ - $C_4$ )-(alcoxy en  $C_1$ - $C_4$ )-carbonyloxy;

R<sup>4</sup> est H, OH, un groupe alcoxy en C<sub>1</sub>-C<sub>4</sub> ou acyloxy en C<sub>1</sub>-C<sub>4</sub> et est situé en position 1 ou en position 2:

20 R5 est OH, un groupe alcoxy en C1-C4 ou acyloxy en C1-C4;

T est un hydrogène ou un groupe alcoxy en  $C_1$ - $C_4$ ; ou sont les sels pharmaceutiquement acceptables de ces composes.

7. Composition selon la revendication 1, dans laquelle, dans la formule, les variables sont telles que définies dans le tableau suivant :

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	Composé	<u>x</u>	R i	_R <sup>2</sup>	<u>_</u> 8 <sup>3</sup>	<u>.*</u> 4	s	<u> </u>
					•			
5	1	5	н	H	11	H	Н	Н
	2	\$	He	2-1-8u	4-1- <b>84</b>	H	н	1- <b>CH</b>
	3	5	Ne	2-t-8u	4- t -8u	н	H	1-CMe
	4	\$	Me	2-1- <b>8</b> 4	4-t <i>-</i> 8u	H	H	1-0Ac
10	5	S	Aç	2-1- <b>Su</b>	4-t-8u	H	Ħ	1- <b>0</b> H
	6	\$	н	2-t-8u	4-1- <b>8</b> 4	н	н	1-CMg
	7	5	н	2-1-84	4-1-8u	H	н	1-0Ac
16	8	0	H	2-t-8u	4-t-8u	н	н	1-04
	•	s	CH <sub>2</sub> CAc	2-t-84	4-t-8u	Ħ	H	1-04
	10	5	н	1-01	н	И	14	3- <b>CH</b>
	11	s	М	1-01	11	11	11	3-QAc
20	12	s	н	1-01	н	И	Iŧ	3-0Me
	13	S	Mg.	1-01	H	H	н	3-CH
	14	s	Me	1- <b>C1</b>	н	H	н	3-0Ac
25	15	s	He	1-01	н	н	н	3-CMe
	16	\$	CH <sub>2</sub> OAc	1- <b>C1</b>	н	H	н	3-CP4
	17	5	CH <sub>2</sub> CAC	1-01	н	н	11	3-0Ac
30	18	0	×	1-01	H	11	:;	2-01
	19	٥	Ne	1-01	н	H	н	3-OH
	20	0	He	1-01	н	н	н	3-0Ac
	21	0	Ne	1-61	11	11	н	3-OMe
35	•	-	-					

	Composé	X	<u>R</u> 1	<u>R</u> 2	R <sup>3</sup>	<u>*</u> 4	R <sup>5</sup>	<u> </u>
5	22	0	Ac	1-01	H	H	н	3-0Ac
	23	0	CH <sub>2</sub> OAc	1 <b>-C</b> 1	Н	H	H	3-CNe
	24	Se	Ne	1-01	H	H	H	3-040
10	25	50	н	1-01	ti	11	И	3-QH
	26	<b>SO</b>	н	1-01	H	11	H	3-0%
	21	<b>SO</b>	H	1-01	11	id	11	3-0Ac
15	28	<b>SO</b>	Re	1-01	н	H	H	3-011
15	29	SO	He	1 <b>C1</b>	н	н	11	3 544
	30	<b>SO</b>	Me	1-01	H	н	Н	3-CMe
	31	so <sub>2</sub>	н	1-01	H	н	H	3-CH
20	32	502	н	1-01	и	11	11	3-0Ac
	33	so <sup>2</sup>	н	1-01	н	H	H	3-CM
	34	so2	He	1-01	H	H	н	3-04c
25	35	502	He	1-01	1-00H2002H	н	H	3-QAc
	36	so	Me	1 C1	н	н	Н	3 0%
	37	502	Ac	1-01	н	H	H	3-04
20	38	502	Ac	1-C1	н.	н	Ħ	3-CAc
30	39	50,	Ac	1-01	н	н	H	3-0%
	40	50	Ac	1-01	н	н	н	3-01
	41	so	Ac	1-01	н	H	H	3- <b>0Ac</b>
35	42	\$0	Ac	1 ¢1	H	H	н	3 -OPA:
	43	50 <sub>2</sub>	CH <sub>2</sub> CAc	1-01	н	н	H	3-CM
	44	502		1-01	н	H	H	3-0Ac
40	45	502	CH <sup>2</sup> CAc	1-01	н	н	H	3-0%
	46	s	CHZIP	11	H	11	П	н
	47	S	Me	н	11	11	Н	15

	Composé	_X	<u>R</u> 1	<u>R</u> 2	_R <sup>3</sup>	R <sup>4</sup>	<u>_</u> 8	T
5	48	\$	Ac	н	н	н	н	н
	49	\$	CH <sub>2</sub> CAc	н	н	н	н	н
	50	0	н	H	Н	н	н	н
10	51	0	He	H	н	н	11	<b>!</b> 1
	52	0	Ac	н	Н	Н	11	н
	53	Se	н	н	н	ш	11	11
15	54	Se	He	н	н	н	11	н
	55	5e	Ac	н	н	н	н	н
	56	Se	Ac CH <sub>2</sub> OAc	н	Н	н.	н	н
•	57	so	н	H	н	н	11	H
20	58	so	Me	н	H	н	н	11
	59	so <sub>2</sub>	Ac	Я	H	н	н	Н
	60	s	н	н	Н	H	14	3-QH
25	61	\$	H	н	н	н	н	3-0Ac
	62	S	H	H	Ħ	Н	н	3-0Me
	63	S	Me	н	н	H	н	3-0Ac
30	64	S	Me	н	H	18	П	3-CH
-	65	S	Ne	H	н	П	11	3-OMe
	5 <b>6</b>	S	K	H	H	H	11	2-CH
0.5	67	S	AC	H	н	н	Ħ	3-QAc
<b>35</b> .	68	\$	Æ	H	H	H	H	3-ONe
	69	S	CH <sub>2</sub> CAC	H	<b>)</b>	н	H	3-CH
	70	\$	CHICAR	H	H	H	H	3-0Ac
40	71	\$	CHZOAC	H	Ħ	H	н	3-0 <del>1/2</del>
	12	Identiqu	se aux con	posés 6	0-71 mais	x=0		
	73	Identiqu	ie aux con	nposés 6	0-71 mais	X=Se		
45	74	\$	×	4C1	н	H	н	3-Q1
	75	5	H	4-C1	H	н	н	3-CMe
	76	5	H	4-01	H	H	Н	3-0Ac

	Composé	X	<u> </u>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	<u>_</u> \$	<u> </u>
5	17	S	Me	4-C)	Н	H	н	3-011
	78	\$	rte	4-C1	H	H	н	3-0Ac
	19	S	*e	4-C1	н	н	H	3-OMe
10	80	S	Ac	4-C1	н	H	H	3- <b>OH</b>
	81	\$	Ac	4-C1	н	· <b>H</b>	H	3-0Ac
	82	S	Ac	4-C1	н	н	H	3-0Me
	83	S	He	4-C1	H	н	н	3-0-82
15	84	S	ne .	4-C1	н	н	н 3-ф	200H(Me)
	85	s	Me .	4-C1	н	н		CC (Ne) 3
	86	205	н	4-C1	П	11	H	3-ca
20	87		н	4-QH	п	Ħ	н	3-OH
	85	-	н	4-C1	н	11	11	3-0Ac
	89	=	н	4-C1	H	H	H	3-CMe
25	90	·='	Ne .	4-C1	н	н	н	3-011
	91	_	He	4-C1	н	н	H	3-CAc
	92	soz	Me	4-C1	H	H	Н	3-che
	93	so <sub>2</sub>	Ac	4-C1	H	н	Ħ	3-011
30	94	so <sub>2</sub>	Ac	4-C1	H	H	н	3-CAc
	95	502	Ac .	4 C1	н	H	Н	3 ONL
	96	\$	CH <sub>2</sub> CAC	4 C1	н	H	H	11
35	97	S	CH <sup>2</sup> OVC	4-01	н	н	Ħ	3 (31
	98	\$	CH <sub>2</sub> CAc	4-C1	H	н	Н	3 CAc
	99	S	CH <sub>2</sub> OAc	4-C1	н	H	H	3-CNe
40	100	502	CH <sup>2</sup> CAc	4-C1	н	H	H	1 ж
	101	502	CHŽOAC	4-C1	н	Я	н	3 CAC
	102	505	CH <sub>2</sub> CAc	4_C1	H	н	11	3-0 <b>%</b> e
	103	Identique	aux comp	osés 74	-103 mais	x=so		
45	104	Identique	aux comp	oses 74	-103 mais	X=0		
	105	Identique	ашх сотр	osés 74	-103 mais	R <sub>4</sub> est	7-C1	

	Composé	x	<u>_</u> R <sup>1</sup>	<u>R</u> 2	R <sup>3</sup>		<u></u> \$	<u> </u>
5	106	Identi	que au co	mposé 105	mais X=0			
	107	Identi	que aux c	omposés 74	-103 mai	a R <sub>4</sub> e:	st 7-OMe	
	108	Identi	que au co	mposé 107	mais X=O		•	
	109	Identi	que aux c	omposés 74	-103 mai	s R <sub>4</sub> e	st 7-(C <sub>1</sub> -	C <sub>6</sub> alkyl)
10	110	Identi	dne en co	mposé 109	mais X=0			
	111	Identi	que aux c	omposés 74	-103 mai	s R <sub>4</sub> e	at 7-(COM	e)
	112	Identi	que au co	mposé 111	mais X=0			
15	113	Identi	que aux c	omposés 74	-103 mai	s R <sub>4</sub> e.	st 7-((CH	2)mCOOR), où
		m est						
	114	Identi	que au co	mposé 113	mais X=0			
20	115	Identi	que aux c	omposé 74-	103 mais	R <sub>L</sub> es	t 9-C1	
	116	S	н	4-Et	H	н	н	3-OH
	117	\$	Ne	4-Et	н	н	н 3	-000001,Ph
	118	S	Ne	4-Et	н	H	Н	3-OAc
25	119	S	Me	4-Et	н	н	н	3-Offe
	120	S	н	4-0£t	H	н	н	3-OH
	121	\$	H	4-0Et	н	н	н	3-CHe
30	122	S	He	4-0Et	H	H	н	3-CM
	123	S	Ne	4-0Et	H	н	н	3-0Ac
	124	S	н	2-0Et	1-OEL	н	н	3-OH
35	125	5	н	2-0Et	1-0Et	H	н	3-0Me
	126	S	Me	2-0Et	1-0Et	н	н	3-0 <del>11e</del>
	127	\$	Me	2-0Et	1-0Et	H	н	3-0 <b>4c</b>
	128	5	н	н	н	н	H	3-GAc
40	129	\$	Me	н	H	н	3-Ac	н
	130	5	Ac	н	H	н	3-Ac	3-CAc
	131	\$	н	7-Ac	H	н	3-44	н
45	132	s	He	7-Ac	н	н	3-Ac	н
	133	\$	Ac	7-Ac	н	н	3-Ac	н

	Composé	x	1	2	R <sup>3</sup>	<u>R</u> 4	<u></u> S	1
_	134	\$	GL 64-	7-Ac			3.44	ш
5			 CH <sup>2</sup> 046		H	н	3-Ac	H
	135	\$	H 	2-40	4-¢1	H	н	3-QH
	136	\$	**	2-14	4-C1	H	н	3-0Ac
10	137	\$	H	7- <b>/4</b>	2-Me	H	<b>H</b>	3-OH
	138	\$	Me .	1-Me	2-He	H	H	3-0Ac
	139	S	н	2-0Et	4-G1	H	н	3-01
15	140	S	%e	2-0Et	4-C1	н	H	3-0Ac
15	141	S	H	2-5-n-8u	4-C1	н	H	3-CH
	142	S	Ne	2-5-11-80	4-C1	н	H	3-GAC
	143	\$	Me	4-5-n-8u	н	н	H	3-0Ac
20	144	5	Ne .	2-0-%	4-8r	н	H	3-0Ac
	145	S	Me	2-0-70	4-C1	н	Н	3-0Ac
	146	\$	Me	2-0-Me	4-8r	Н	Н	3-01
<i>2</i> 5	147	\$	н	2-0-14	3-0H	н	H	7-Q <b>Me</b>
25	148	\$	H	1-che	3-CH	н	H	7-CHe
	149	S	н	2-cme	3-OH	1-8r	н	7-UMB
	150	S	н	1-044	3-QH	2-8r	H	1-one
30	151	5	н	1-0Me	3- <b>0</b> H	4-8r	н	7 -0%e
	152	S	н	1-CMe	3-QH	2-C1	н	1-che
	153	s	H	1-Otte	3- <b>O</b> H	4-C1	H	7-UNC
35	154	\$	H	2-0Me	3-04	1-C1	H	7 -OMC
	155	s	н	2-0%	3- <b>OH</b>	4-C1	H	1-che
	156	s	н	2-0Et	3-OH	1-8r	н	1-OEt
	157	s	н	2-0Et	3-CH	4-8-	н	7-0Et
40	158	\$	н	2-0£t	3-04	r'-c1	Н	1-0£1
	159	\$	н	2- <b>0</b> £1	3-OH	<b>4</b> _C1	н	1-0EL
	160	5	н	2-CMe	3- <b>OH</b>	1-8 <b>r</b>	7-CHe	
45	161	5	H	2-0Me	3-OH	4-Br	7-0Me	

	Composé	¥	<u> </u>	R <sup>2</sup>	R <sup>3</sup>	<u></u> 4	<u> </u>	1
5	162	S	н	2-Offe	3-OH	4F	H	1-0 <del>10</del>
	163	\$	н	2-0Me	3-OH	LOF <sub>3</sub>	н	1-cne
	164	\$	н	2-CHe	3-OH	4-8r	н	1-0Et
10	165	S	н	2-CMe	3-OH	4C1	н	1-0EL
10	166	\$	н	2-OMe	3-OH	4F	н	7-0Et
	167	S	н	2-0 <del>14</del>	3- <b>CH</b>	4-[	н	7-che
	:68	S	н	2-CMe	3- <b>CH</b>	LOF3	H	7-Oct
15	169	5	H	2-0Et	3-CH	4-8r	H	1-CHe
	170	\$	н	2-0E t	3- <b>CH</b>	4 <b>-</b> C1	Ħ	1-che
	171	\$	н	2-0Et	3-OH	<b>4</b> _F	н	7-CNe
20	172	S	н	2-0Et	3-OH	4-053	H	1-CMe
	173	S	н	1-cre	2-CMe	3-CH	4-8r	1-CHe
	174	s	н	1-0Me	3- <b>CH</b>	н	н	2-CMe
25	175	S	н	1-044	3-CH	4-8r	н	2-CMe
20	176	Identio	que aux co	mposés l	47-175 ma	is X=O		
	177	Identic	que aux co	mposés l	.47-175 ma	ie X=SO		
	178	S	H	2-5Me	3-04	4-8r	Н	1 -GMe
30	179	S	H	2-0Mg	3- <b>CH</b>	4-8r	7-SMe	
	180	50 <sub>2</sub>	H	2-502	<b>№</b> 3-OH	4-85	H	1-che
	181	Identi	que aux co	omposés l	47-175 ma	is X=SO		
35	182	S	H	4-C1	H	H	H	3-06z
	183	\$	н	4-01	н	H	н 3-	000001(Me) 2
	184	\$	Ac	Н	н	1-4	11	3-0Ac
40	185	\$	Me	H	н	7-Me	н	3-CHe
40	186	\$	н	Н	H	7-5	n	3-0Ac
	187	5	Me	H	н	9-C1	н	3-0%e
	188	\$	Me	н	н	9-C1	Н	3-0Ac
45	:89	\$	Me	н	н	7-74	11	3-CAC

	Composé	¥	<u>*</u> 1	<u>R</u> 2	_R <sup>3</sup>	<u>.*</u> 1	<u></u> 5	f
5	100							
	190	S	н	Я	11	9-C1	Н	3-0Ac
	191	\$	н	<b>H</b>	4-03	H	Н	3 UAC
	192	\$	H	<b>H</b>	4-01	H	H	3-01\$
10	193	S	Ac	н	1-C1	1-#	H	3-cHe
	194	S	Ac u -	н	1-01	1-5	Н	3-QH
	195	\$	Me	H	4-C1	7-5	H	3-0Me
15	196	so	н	Н	H	11	11	3 OAL
	197	205	н	H	н	н	11	3 CAC
	198	s0 <mark>2</mark>	н	Н	н	11	11	3 04
	199	205	н	н	Н	1-5	П	3-GAc
20	200	s0 <sup>2</sup>	H	н	4C1	H	H	3-01s
	201	\$	н	1-Offe	2-OMe	4-Mg	H	3-OH
	505	S	н	1-cHe	2-0Me	4-No	H	3-OAc
25	203	502	н	1-GHe	2-CMe	4-Me	H	3-OH
	204	502	н	4-orte	П	и	И	3 ⊅:
	205	5	Я	2-0Me	3-CH	4-8r	1-CMe	H
30	206	\$	н	2-CPe	3-0Ac	4-8r	1-che	н
	201	\$	н	2-CMe	3-OAc	4-C1	1-CHe	н
	208	502	н	2-cre	3-OH	4-8r	7-CMe	н
	209	s	н	2-Offe	3-0Ac	1-CHe	4-8r	н
35	210	\$	н	2-CMe	3-0Ac	7-0He	4-Br	H
	211	S	H	2-CMe	3-082	1-CMe	4-8r	н
	212	S	Ne	2-0 <b>4e</b>	3-Offe	1-CMe	4-87	H
40	213	S	н	2-CMe	3-cife	7-CHe	4-8-	H
	214	S	Ac	2-cme	3-CAc	7-CMe	4-8r	H
	215	\$	Ac	2-0 <b>%</b> e	3-OH	7-0 <del>14e</del>	4-8r	н
	2 '6	S	AC.	2-0Me	3-456	1-0%e	4-ar	н
45	217	S	**	2 ~ Ae	3-CAc	1-0Me	4-3r	н

	Composé	<u>x</u>	<u>R</u> 1R		<u>8</u> 3	4	_R <sup>S</sup> 1	·
6	21 <b>8</b>	5	Me	2-0 <del>14e</del>	3-CH	7-0%	4- <b>3</b> r	×
	21 <del>9</del>	s0 <sub>2</sub>	н	2-CM	3-QH	7-CMe	4-8r	H
	220	so	н	2-044	3-QAc	1-0%	4-8r	H
10	221	so <sub>2</sub>	н	2-CMe	3-0Ac	7-04	4-8r	н
	222	SQ.	н		3-0Ac	7-CHe	4-Br	н
	223	so	н	2-CHe	3-0Ac	7-0Me	4-8r	н
5	224	s	н	2-CNe	3-000 <sub>2</sub> Me	4-8r	7-CHe	H
	225	\$	н		3-000 <sub>2</sub> Et	4-Br	7-0Me	я
	226	\$	H		_			н
	227	S	н		3-000 <sub>2</sub> UI(Ne)0Ac			н
0	228	s	∞ <sub>2</sub> ne	2-CNe	-	4-8r	7-0He	н
	229	\$	α <sub>2</sub> ει	2-CFe		4-8r	7-CMe	н
	230	\$	2 صاراته) هد			4-8r	7-CHe	H
5	231	S	ळ <sup>2</sup> टम(५०)व्हर			4-C1	7-0Me	н
	232	\$	യ <sup>2</sup> CH(He)0Ac	2-CMe	3-QH	4.5	7-0#e	н
	233	\$	co <sup>5</sup> ch(se)ove			4-ar	7-OFe	н
80	234	\$	-		3-000 <sub>2</sub> 0H(Me)0Ac		7-Offe	H
	235	0	Ac	2-UN		4-8r	7-QMe	я
	236	0	Ac	2-CMe		4-8r	7-0Me	н
	237	0	00 <sub>2</sub> CH(Ne)0Ac			4-8r	7-CP4	H
ì5	239	0	∞³cH(₩)ove	2-Offe		4-8r	7-OMe	н
	239	s	H	2-0Me		4-8r	7-Me	н
	240	\$	H	2-0Me		4-85	7-He	H
40	241	S	H	2-CMe		4-6r	7_F	Ħ
	242	5	н	2-CMe		1-8r	7_\$	Ħ

-	Compos	<u>é x</u>	<u>.</u> 1_	¥ş.	£3	14.	<u>.</u> 5_	Ţ
5	243	s	H	H	tl	н	H	OCOEt
	244	S	H	2-C1	3 <b>-</b> C1	H	11	013)-n-Pr
	245	\$	н	H	4-C1	H	H	000-n-8u
10	246	s	н	1-80	H	H	H	H
,,	247	5	н	2-OF <sub>3</sub>	н	H 1	11	11
	248	5	H	2-Et	н	H	H	#
	249	5	H	H	3- <b>C</b> 1	7-0%	H	H
15	250	\$	H	H	3 <b>-</b> C1	1-01	H	H
	251	\$	н	Н	3-NO <sub>2</sub>	11	7-402	н
	252	\$	н	3-NMe <sub>2</sub>	11	U .	7-NMe <sub>2</sub>	H
20	253	\$	н	1-01	11	:1	H	Н
	254	S	н	3-OAc	1 ·F	н	11	11
	255	\$	H	3-CH_COMe	4-C1	16	Н	Н
25	256	s	H	3-0000144		4-C1	н	H
20	257	\$	Ac	3-CMe	4-C1	H	н	H
	258	0	н	2 -CF <sub>3</sub>	H	н	н	H
	259	S	Me	Н	3-QMe	н	4-C1	н
30	260	50 <sub>2</sub>	H	4-C1	3-01	н	н	H
	261	5	He	1- <b>F</b>	4-C1	3-CMe	н	н
	262	\$	He	3-0 <del>1/e</del>	7-14	H	H	И
35	263	S	Ac	4-C1	Ħ	Н	H	Ħ
	264	5	Ac	3-GAc	4-01	н	H	н
	265	, so	Ac.	4-C1	н	н	н	3-OH
40	26 <b>6</b>	. so <sup>5</sup>	Ac	4-Ç1	н	н	н	3 OAc E
40	267	50,	Ac	4-8r	н	H	н	3-CAc

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	Compose	<u>é</u> ₹	¥1_	R <sup>2</sup> _	43 <sub>-</sub>	<u>R</u> 4	4 <sup>5</sup> _	Ī
5	268	205	CO2CH(He)OAc	4-C1	н	H	н	3-OH
	26 <del>9</del>	\$0 <sub>2</sub>	H	<b>4</b> -c1	н	н 3-00	D <sub>2</sub> CH(Me)OAc	н
10	210	0	Ac	4-01	н	11	н	2 OAc
	271	0	CONTROL CAC	4-C1	н	н	н	3-OH
15	212	0	ක <sup>2</sup> cH(%)0%c	4 -C1	н	H	Ħ	3 O/C
20								
	213	0	Н	4C1	н	11 3-0	ක <sup>2</sup> CH(Jee) 0Ac	Н
25	214	s	CH <sub>2</sub> OAc	4-C1	н	н	н	3-U/C
	275	\$	CH(Me)OAc	4-C1	н	H	н	3-0Ac
30	276	5	н	2-CMe	3-UH	1-CH	н	П
	217	\$	H	2-CMe	3-CH	7- <b>QH</b>	4-8r	н
35	278	\$	н	2-Offe	3-0Ac	7- <b>0</b> H	4-8r	н
	219	\$	н	2-CMe	3-0Ac	7-0Ac	4-8r	н

	Composé	Ĩ	<u>R</u> 1_	Ĕ2_	<u>8</u> 3	<u>R</u> 4_	<u>.</u> 5	Ţ
5	2 <b>80</b>	S	Aç	2 -CHe	3-OH	7- <b>O</b> H	1-8r	н
	281	5	Ac	2-CMe	3-0Ac	1-OH	4-8r	н
	2 <b>82</b>	\$	Ac	Z-CMe	3-0Ac	1-0Ac	4-8r	н
10	283	\$	Ac	2-014	3-OH	7-0Ac	4-8r	н
	284	soz	Ac	2 -CMe	3- <b>0</b> H	4-8r	7 -QMe	н
	285	so	CO_CH(Ne)CAc	2-CMe	3-0Ac	4-8r	7 -CNe	н
15		•	•		н			
	286	502	Ac	2 -CMe	H   1   3-000 <sub>2</sub>   COAc   He	4-8r	1-0Me	H
20					-			
	287	so <sub>2</sub>	Ac	2-0Me	3-0Ae	4-8r	7-CHe	Н
25	288	so <sub>2</sub>	COZCH(Fe)CAC	2-GMe	3-OH	4-8r	1-CMe	H
	2 <b>89</b>	s	Ac	2-0Et	3-0Ac	4 <b>-</b> C1	н	н
30	290	S	Ac	2-0Et	3-OH	4-C1	н	н
	2 <b>9</b> 1	S	Me	н	1-Ac	н	н	3 -Cite
	292	5	Me	н	н	1-F	н	3-CMe
	293	S	Ac	н	н	1-F	н	3-CNe
35	294	S	Ac	н	н	1-4	н	3-OH

- 8. Composition selon la revendication 7, dans laquelle le composé répond à l'une des formules numérotées 13, 14, 31, 37, 38, 73, 76, 78, 79, 80, 81, 82, 84, 86, 87, 88, 92, 93, 94, 124, 139, 147, 151, 153, 155, 157, 159, 162, 163, 164, 165, 169, 170, 178, 179, 182 à 223 inclus, 225 à 242 inclus, 260 ou 267 à 294 inclus.
- 9. Composition selon la revendication 7, dans laquelle le composé répond à l'une des formules numérotées 79, 80, 81, 86, 88, 93, 94, 197, 198, 214, 215, 226, 230, 233, 235, 236, 237, 275, 280, 283, 284, 287, 288, 289 et 290.
- 10. Composition selon la revendication 1, utilisable pour (a) inhiber la biosynthèse ou l'action de leucotriènes chez les mammifères; (b) traiter les maladies cardiovasculaires; (d) traiter l'inflammation; (d) traiter les allergies; (e) traiter la douleur; (f) traiter l'asthme; ou (g) traiter les troubles de la peau.
  - 11. Composés de formule :

dans laquelle les substituants sont tels que définis dans le tableau suivant :

15	Composé	Ā	<u>R</u> 1_	¥2_	R <sup>3</sup> .	<u>8</u> 4_	4 <sup>5</sup> _	<u>t</u>
	3	`s	He	401	н	Ħ	н	3-CM
	8	\$	Ac.	4-C1	H	H	н	3-0Ac
20	9	S	Ac	4-01	H	н	н	3-OH
25				·				
	Composé	Ĭ	<u>*</u> 1_	ë <sub>s</sub> -	¥3_	<u>.</u>	Ŗ <sup>5</sup> _	Ţ
30	21	\$	Ac	н	4-C1	1-5	H	3-0Me
	28	\$	Ac	H	4-C1	1-5	H	3-04
	29	\$	Ne	н	4-01	14	H	3-0%
35	30	\$	H	H	2-0Et	4-01	H	3-CH
	32	50 <sub>2</sub>	H	н	H	H	н	3-0Ac
	33	۶٥,	H	н	4-¢1	H	н	3-0Ac
40	34	so,	H	H	4-01	H	H	3-OH
	39	\$	н	1-ONe	2-Offe	4-14	H	3-QH
	40	\$	H ,	1-0%	2-0Me	4-74	H	3-0Ac
45	41	so,	н	1-0%	2-0Me	4-110	H	3-OH

	Composé	Ā	81.	8 <sup>2</sup> -	ž <sup>3</sup> .	¥4_	<u>.</u> 5.	1
5	43	\$	н	1- <b>QH</b>	2-C(Ne) <sub>3</sub>	H 4-	C(Me) <sub>3</sub>	H
	19	SO	H	1-QNe	2-0Me	4-16	н	3-CH
	SO	30	н	1-GHe	2-OMe	4-He	н	3-CAc
10	51	so <sub>2</sub>	н	1-QNe	2-0%e	4-14	H	3-OAc
	52	s	н	2-0ffe	3-OH	4- <b>8</b> r	7-0fe	H
	53	\$	н	2-Offe	3-OH	4-C1	7-0%s	H
15	54	5	H	2-014	3-0Ac	4-8r	7-ONe	H
	55	S	н	2-0Me	3-0Ac	4-C1	7-0Me	H
	56	502	Н	2-0Me	3-OH	4-8r	7-074	H
20	58	so,	Н	2-OMe	3-0Ac	4-Br	1-one	н
20	59	٥	Ac	2-0Me	3-CH	4-8r	7-0He	H
	60	0	Ac	2-0Me	3-0Ac	4-8r	7-0Me	H
	61	0 co,	OH (Ne) OAc	2-0 <b>%</b>	3-OH	4-8r	7-014	H
25	62	•	CH(Ne)CAc			4-8r	7-Offe	H
	63	s	<b>н</b>	2-0Me	3- <b>CH</b>	4-8r	7-14	H
	64	\$	H	2-OF4e	3-0Ac	4-\$r	7- <b>Pe</b>	H
30	65	\$	н	2-Offe	3 <b>-</b> QH	4- <b>3</b> r	1-5	н
	66	S	н	2-OMe	3-0Ac	4- <b>3</b> r	1 <b>-F</b>	H
	67	so	н	2-0Me	3-OAc	1-8r	1-0Ne	H
35	68	so <sub>2</sub>	н	2-Offe	3-OH	н	7-Offe	H
	69	30,	н	2-0Me	3-0Ac	н	7-0F4	H
	70	s	Ac	2-0Me	4-8r	7-Office	н	3-0Ac

	Composé	Ā	<u>R</u> 1_	5 <u>.</u>	<u>R</u> 3	<u>R</u> 4	g <sup>5</sup> _	Ī
5	71	S	Ac	2-CHe	4-C1	7-GMe	н	3-0Ac
	12	S	Ac	2-0Me	4_F	7-CMe	н	3-0Ac
	73	5	Ac	Z-CMe	4-I	1-CHe	Я	3-0Ac
	74	s	Ac	2-CMe	4-053	7- <b>OMe</b>	H	3-0Ac
10	75	\$	Ac	2-CMe	4-CN	7-CHe	н	3-0Ac
	76	S	Ac	2-0Et	4-8r	1-0Et	H	3-0Ac
	77	5	Ac	2-0Et	4-C1	7-0Et	н	3-OAc
15	78	S	ÀC	2-014e	4-8r	1-0Et	н	3-0Ac
	79	\$	Ac	2-CMe	4-C1	1-0Et	н	3-0Ac
	80	3	Ac	2-CMe	4-F	7-0Et	н	3-OAc
20	81	5	Ac	2-0Et	4-8r	7-0He	H	3-0Ac
	82	S	Ac	2-0Et	4-C1	7-CHe	н	3-0Ac
	83	\$	Ac	2-0Et	4-F	7-QNe	н	3-0Ac
	84	S	Ac	2-0Et	4-CF <sub>3</sub>	7-0He	Н	3-OAc
25	85	s	н	2-0Me	4-80	1-CHe	H	3-OH
	86	S	Ħ	2-CMe	4-C1	7CMe	H	3-OH
	87	S	н	2-0Me	4-F	7-OMe	H	3-OH
30	<b>38</b>	S	н	Z-CMe	4-CF <sub>3</sub>	7- <b>04e</b>	H	3-OH
	89	S	H	2-CHe	4-85	1-CHe	H	3-0Ac
	90	S	н	2-CMe	4-8r	1-CHe	H	3-08z
35	91	\$	н	2-CMe	4-8r	1-0Me	Н	3-0000HHe <sub>2</sub>
	92	\$	н	2 -CMe	4-8r	1-0He 3-	och <sup>5</sup> co <sup>5</sup> H	H
	93	\$	Ac	2 -0Me	4-8r	1-CHe	н	3-78z
	94	S	Ac	2 -CMe	4-Br	1-che	н	3-CMe
40	95	\$	Ac	2.40Me	4-8r	7-CMe 3-	och₂co²H	H
	36	3	Ac	2-0Me	4-61	7-0Me 3-	ಎಂಸ <sub>ತಿ</sub> ಂಶಿ <sub>ಗ</sub>	H
	91	5	CH_CAC	2-0He		7-0Me	н	3-OH
45	38	3	CHZCAC	2-0% <b>e</b>	4-C1	7-CHe	н	3 -CH
	39	5	CH_CAC				н	3-CAc

	Composé	Ã	<u> </u>	¥2_	R <sup>3</sup>	<u>R</u> 4	<u> </u>	<u>r</u>
5	100	\$	CH <sub>2</sub> OAc	2-CMe	4-Br		н	3-08z
	101	\$	CH <sub>2</sub> OAc	2-0Me	4-8r	7-0 <del>14e</del>	н	3-0Me
	102	S	оч <sup>2</sup>				н	3-OH
10	103	s	여				н	3-0Ac
70	104	5			4-C1		н	3-OH
	105	S	He	2-0Me	4-F	1-0Me	H	3-CH
	106	\$	Me	2-0Me	4-CF <sub>3</sub>	7-0Me	H	3-OH
15	107	5	CH(Me) CAc	2-OMe	4-8	7-0Me	H	3-OH
	108	S CH(	(Me) 0C0C (Me) 3	2-0Me	4-8r	7-0 <del>110</del>	H	3-OH
	109	\$	CH(Me)OAc	2-0 <del>1/e</del>	4-C1	7-ONe	H	3-OH
20	110	S	CH(Me)OAc	2-0Me	4-F	7-0He	н	3-OH
	111	\$	CH (Me) OAc	2-0Me	4-CF <sub>3</sub>	1-0fe	н	3-OH
	112	S	H	2-Offe	4-8r	7-0Me	3-000 <sub>2</sub> Me	н
25	113	5	H	2-QMe	4Br	7-0 <del>11e</del>	3-000 <sub>2</sub> Et	н
	114	5	н	2-CMe	4-8r	7-OMe	3-000 <sub>2</sub> CH (Me)	OAC H
	115				4-C1		3-000 <sup>2</sup> CH(Me)	OAC H
	116	\$	∞ <sub>z</sub> ne	2-OMe	4-Br	7-0%	H	3-OH
30	117		ω <sub>2</sub> ει				н	3-OH
	118		CO_CH(He)OAc					3-CH
	119	S	CO_CH(Ne)OAc	2-014	4-C1	7-Offe	н	3- <b>CH</b>
35	120	\$	00_CH(Me)0Ac	2-0Me	4 <b>-</b> F	7-OMe	H	3-OH
	121	\$	CO_CH(Me)OAc	2-0Me	4-8r	7-Offe		3-04¢
	122	\$	COZCH(Pe)CAc	2-0 <b>Me</b>	4-8r	7-OMe	3-000 <sup>2</sup> CH(Me	)OAC H
40	123	5	Ac '	2-0Me	4-8r	7-QMe	H	3-CH
-	124	\$	Ac	2-OMe	4-C1	7-0Me	н	3- <b>QH</b>
	125	\$	Me	2-OMe	4-8 <b>r</b>	7- <b>0%e</b>	н	3-014
	126	S	н	2-044	4-Br	7-OMe	H	3-CMe
45	127	S	CH(Me)OAc	4-C1	H	н	н	3-OAc
	128	50,	Ac	4-C1	н	H	н	3- <b>O</b> H

·	Composé	ž	¥1.	<u> </u>	£3_	<u>B</u> 4_	š	<u>t</u>
5	129	so,	Ac	4-C1	, <b>H</b>	н	H	3-0Ac
	130	5	Ac	2-Œt	4-C1	H	H	3-CH
	131	\$	Ac	2-0Et	4-C1	H	И	3-0Ac
10	132	\$	Ac	2-ONe	4-Br	7- <b>OH</b>	н	3-CH
10	133	\$	Ac	2-0 <del>1/e</del>	4- <b>\$</b> F	7-0Ac	H	3-OH
	134	50 <sub>2</sub>	Ac	2-0Fe	4—8r	7-ONe	H	3-OH
	13\$	so,	Ac	2-OF##	4- <b>&amp;</b> r	7-OFe	Н	3-0Ac
15	136	50,	002CH(Ne)0A	c 2-OMe	4-8r	7-QNe	H	3-OH
	137	s	ထွင္ပတ္ထာ	H	4-8r	7-OMe	2-0 <del>11e</del>	3- <b>0</b> H
			He C(Me	<sup>)</sup> 3				
20	138	\$	H	2-0Me	4-1	7- <b>0%</b>	H	3- <b>CH</b>
	139	S	H	2-OMe	4-CI	7-Qffe	Н	3-0H
	140	\$	H	2-0Et	4 <b>-</b> 8r	7-0Et	Н	3CH
25	141	S	H	2- <b>0</b> Et	4-C1	1-0Et	Ħ	3-CH
	142	5	H	2-Offe	4-8r	7-0Et	H	3-04
	143	\$	H	2-Offe	4-C1	7-0Et	н	3-CH
	144	s	M	2-0 <del>1/e</del>	4F	.1-0Et	H	3- <b>Q</b> H
30	145	\$	H	2-0Et	4- <b>8</b> r	7-0 <del>1/e</del>	H	3-04
	146	S	н	3-0E#	4-C1	7- <b>0%</b>	H	3- <b>CH</b>
	147	S	н	2-0Et	4-5	1-0Ne	H	3-CH
35	148	\$	H	2-0Et	4-073	1-070	H	3-CH

- 12. Composés dont les variables dans la formule I sont numérotées 3, 8, 9, 32, 33, 34, 41, 59, 60, 6i, 70, 71, 114, 118, 119, 121, 123 ou 127 à 137 inclus dans la revendication 11.
  - 13. Composés dont les variables dans la formule I sont numérotées 70, 71, 118, 119, 121, 123 ou 137 dans la revendication 11.
  - 14. Composés selon la revendication 11, de formule :

50

dans laquelle les substituants sont tels que définis dans le tableau suivant :

5 10 15	- <del>д</del> 1 н н н н	R <sup>2</sup> - Br Cl F C <sup>3</sup> 3 Br	QII QH QH QH QAc QCOPh
20	<u>я</u> 1 н	R <sup>2</sup> Br Br	R3 OCOCHMe <sub>2</sub> OCH <sub>2</sub> CO <sub>2</sub> H OAG
25	AC	Cl	OAc
	AC	Br	ocoph
	AC	Br	ome
30	Ac	Br	осн <sub>2</sub> со <sub>2</sub> н
	Ac	Cl	осн <sub>2</sub> со <sub>2</sub> н
	CH <sub>2</sub> OAc	Br	он
35	CH <sub>2</sub> OAc CH <sub>2</sub> OAc CH <sub>2</sub> OAc	Cl Br Br	OH OAC OCOPh OMe
40	CH <sub>2</sub> OAG CH <sub>3</sub> CH <sub>3</sub>	Br Cl	OH OAC OH
<b>4</b> 5	СН <sub>3</sub>	f	он
	СН <sub>3</sub>	Cf <sub>3</sub>	он
	СН (СН <sub>3</sub> ) ОАС	Br	он
5 <b>0</b>	СН (СН <sub>3</sub> ) ОСОС (СН <sub>3</sub> ) <sub>3</sub>	Br	ОН
	СН (СН <sub>3</sub> ) ОАс	Cl	ОН
	СН (СН <sub>3</sub> ) ОАс	F	СН
55	CH (CH <sub>3</sub> ) OAc	CF <sub>3</sub>	OH
	CO <sub>2</sub> CH (Me) OAc	Br	OH
	CO <sub>2</sub> CH (Me) OAc	Br	OAC

15. Composés selon la revendication 11, de formule :

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dans laquelle les substituants sont tels que définis dans le tableau suivant :

	R <sup>2</sup> _	<u>R</u> 3	R <sup>5</sup>
20	Br	OMe	OMe
	cı	OMe	OMe
	F	OMe	OMe
	I	OMe	QMe
25	cr <sub>3</sub>	OMe	OMe
	CN	OMe.	OMe
	Br	OEt	OEt
30	Cl	OEL	OEŁ
	Br	OMe	OEt
	Cl	OMe	OEt
	7	OMe	OEt
35	Br	OEt	OMe
	Cl	OEt	OMe
	F	OEt .	OMe
40	CF <sub>3</sub>	OEt	OMe

- 45 16. 3-Acétoxy-10-acétyl-4-bromo-2,7-diméthoxy-10H-phénothiazine.
  - 17. 10-(1-Acétoxyéthoxycarbonyl)-4-bromo-2,7-diméthoxy-3-hydroxy-10H-phénothiazine.
  - 18. 3-Acétoxy-10-acétyl-4-chloro-2,7-diméthoxy-10H-phénothiazine.
  - 19. 4-Bromo-2,7-diméthoxy-3-hydroxy-10-(1-pivaloyloxyéthoxycarbonyl)-10H-phénothiazine.
  - 20. 3-Hydroxy-10-(1-acétoxyéthoxycarbonyl)-4-chloro-2,7-diméthoxy-10H-phénothiazine.
- 21. 3-acétoxy-10-(1-acétoxyéthoxycarbonyl)-4-bromo-2,7-diméthoxy-10H-phénothiazine.
  - 22. 3-Hydroxy-10-acétyl-4-bromo-2,7-diméthoxy-10H-phénothiazine.

- 23. Composition selon l'une quelconque des revendications 1 à 9, comprenant en outre une quantité efficace d'un second ingrédient actif qui est un anti-inflammatoire non stéroïdien; un agent analgésique périphérique; un inhibiteur de cyclooxygénase; un antagoniste de leucotriènes; un inhibiteur de leucotriènes; un antagoniste de récepteurs H<sub>2</sub>; un agent antihistaminique; un antagoniste de prostaglandine ou un antagoniste de thromboxane.
- 24. Composition selon la revendication 23, dans laquelle le rapport pondéral du composé de formule I au second ingrédient actif est dans l'intervalle de 1000:1 à 1:1000.
- 25. Composition selon la revendication 24, dans laquelle ledit rapport est de 200:1 à 1:200.
  - 26. Composition selon l'une quelconque des revendications 23 à 25, dans laquelle le second ingrédient actif est un anti-inflammatoire non stéroïdien.
- 27. Composition selon la revendication 26, dans laquelle l'anti-inflammatoire non stéroidien est l'indométhacine.

### Ansprüche

20 1. Pharmazeutische Zusammensetzung, die die Leukotrien-Biosynthese oder -wirkung in Säugetieren inhibieren kann und einen pharmazeutischen Verdünner, Träger oder Exzipienten enthält sowie eine Verbindung der Formel I:

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X Se, S, SO, SO<sub>2</sub> oder O ist;

 $R^1$  H;  $C_{1-6}$ -Alkyl; Acetyl;  $(C_{1-6}$ -Acyloxy)- $(C_{1-6}$ -alkyl); Benzoyl; substituiertes Benzoyl mit  $C_{1-3}$ -Alkyl, Halogen, CN,  $CF_3$ ,  $COOR^6$ ,  $CH_2COOR^6$ ,  $(CH_2)_nNR^8R^9$  (worin n 0, 1 oder 2 ist),  $C_{1-3}$ -Alkoxy und/oder OH als Substituent (hier als "substituiert wie hier definiert" bezeichnet); Carbamoyl; CO-NHR<sup>7</sup>;  $COOR^7$ ; p-Toluolsulfonyl; Methansulfonyl; eine Acylgruppe, so daß  $R^1$ -OH eine essentielle Aminosäure ist; Benzyl; Phenethyl;  $(CH_2)_pOR^a$ , worin  $R^a$   $C_{1-6}$ -Alkyl oder Phenyl ist und p eine ganze Zahl von 1 bis 5 ist, wenn  $R^a$  Phenyl ist, und eine ganze Zahl von 1 bis 6 ist, wenn  $R^a$  Alkyl ist;  $(CH_2)_nCOOR^6$ , worin n 0, 1 oder 2 ist; oder  $(C_{1-6}$ -Acyloxy)- $(C_{1-6}$ -alkoxy)carbonyl ist;

jedes von R², R³, R⁴ und R⁵ unabhängig von den anderen Wasserstoff;  $C_{1-6}$ -Alkyl;  $C_{2-6}$ -Alkenyl oder (CH₂) $_q$ M ist, worin q 0 oder eine ganze Zahl von 1 bis 6 ist und H (a) -OR¹6; (b) Halogen; (c) -CF₃; (d) -SR¹6; (e) Phenyl oder substituiertes Phenyl, wie hier definiert; (f) COOR⁶; (g) -CO-R¹⁴; (h) Tetrazolyl; (i) -NH-CO-R³; (j) -NR³R³; (k) -NHSO₂R¹0, worin R¹0 OH,  $C_{1-6}$ -Alkyl,  $C_{1-6}$ -Alkoxy oder Phenyl ist; (1) -CO-CH₂OH; (m) -SOR¹¹, worin R¹¹  $C_{1-6}$ -Alkyl, Phenyl, substituiertes Phenyl, wie hier definiert, (CH₂)-mCOOR⁶, worin m eine ganze Zahl von 1 bis 6 ist, CN, Formyl oder  $C_{1-4}$ -Perfluoralkyl ist; (n) -CONR³R³; (o) -SO₂NR³R³; (P) -SO₂R¹³, worin R¹³ Wasserstoff, OH,  $C_{1-6}$ -Alkyl, Phenyl, substituiertes Phenyl, wie hier definiert, (CH₂)mCOOR⁶, worin m wie oben definiert ist, CN, Formyl oder  $C_{1-4}$ -Perfluoralkyl ist; (q) -NO₂; (r) -O-CO-R¹⁴; (S) O-CO-NR³R³; oder (t) -CN ist; jedes R⁶, unabhängig von den anderen, Wasserstoff,  $C_{1-6}$ -Alkyl oder Phenyl ist;

jedes  $R^7$ , unabhängig von den anderen,  $C_{1-6}$ -Alkyl, Benzyl, Phenyl oder  $(C_{1-6}$ -Acyloxy)- $(C_{1-6}$ -alkyl) ist:

jedes  $R^8$  und jedes  $R^9$ , unabhängig von allen anderen, Wasserstoff,  $C_{1-4}$ -Acyl, Phenyl oder substituiertes Phenyl, wie hier definiert, ist oder ein  $R^8$  und ein  $R^8$  über das N, an das beide gebunden sind, unter Bildung einer heterocyclischen Gruppe mit 5 bis 8 Ringatomen zusammengenommen sind; jedes  $R^{14}$ ,

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unabhängig von den anderen, Wasserstoff,  $(CH_2)_rCOOR^6$ , worin r 0 oder eine ganze Zahl von 1 bis 4 ist;  $C_{1-6}$ -Alkyl;  $C_{1-6}$ -Alkoxy;  $(C_{1-6}$ -Acyloxy)- $(C_{1-6}$ -alkoxy); Phenyl; substituiertes Phenyl, wie hier definiert; oder  $C_{1-6}$ -Aminoalkyl ist, so daß  $R^{14}COOH$  eine essentielle Aminosäure ist;

jedes R<sup>16</sup> unabhängig von allen anderen Wasserstoff,  $(C_{1-5}-Alkoxy)-(C_{1-5}-alkyl)$ ,  $C_{1-6}-Alkyl$ ; Benzyl;  $(C_{1-6}-Acyloxy)-(C_{1-6}-alkyl)$ ; Phenyl; substituiertes Phenyl, wie hier definiert;  $-CH_2)_mCOOR^6$ , worin m wie oben definiert ist; CN; Formyl; Perfluoralkyl; oder  $CH_2-R^{12}$  ist, worin R<sup>12</sup>  $C_{1-5}-Alkyl$ , Dimethylamino oder Phenyl ist;

und T Wasserstoff oder -OR<sub>15</sub> ist, worin R<sub>15</sub> Wasserstoff,  $C_{1-6}$ -Alkyl,  $(C_{1-5}$ -Alkyl)acyl, Phenylacyl, substituiertes Phenylacyl, wie hier definiert; Benzoyl, substituiertes Benzoyl, wie hier definiert; oder Arylsulfonyl ist; sowie Verbindungen, die pharmazeutisch annehmbare Salze davon sind.

- 2. Zusammensetzung nach Anspruch 1, worin in der Formel X<sub>1</sub> S, SO, SO<sub>2</sub> oder O ist und die anderen Substituenten wie in Anspruch 1 definiert sind.
- 3. Zusammensetzung nach Anspruch 2, worin  $R^2$ ,  $R^3$ ,  $R^4$  und  $R^5$  alle verschieden von  $C_2$ - $_6$ -Alkenyl sind.
  - Zusammensetzung nach Anspruch 3, worin in der Formel X S oder O ist;

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R¹ H; C<sub>1-6</sub>-Alkyl; C<sub>1-6</sub>-Acyl; (C<sub>1-6</sub>-Acyloxy)-(C<sub>1-6</sub>-alkyl); (C<sub>1-6</sub>-Alkoxy)-(C<sub>1-6</sub>-alkyl); Benzoyl; Benzoyl; substituiert wie hier definiert; Carbamoyl; CO-NHR<sup>7</sup>; COOR<sup>7</sup>; (CH<sub>2</sub>)<sub>p</sub>OR<sup>a</sup>, worin R<sup>a</sup> C<sub>1-6</sub>-Alkyl oder Phenyl ist und p eine ganze Zahl von 1 bis 5 ist; (CH<sub>2</sub>)<sub>n</sub>COOR<sup>6</sup>, worin n 0, 1 oder 2 ist; oder (C<sub>1-6</sub>-Acyloxy)-(C<sub>1-6</sub>-alkoxy)carbonyl ist;

M, falls in R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> oder R<sup>5</sup> einbezogen, (a) -OR<sup>15</sup>; (b) Halogen; (c) -CF<sub>3</sub>; (d) -SR<sup>16</sup>; (e) COOR<sup>6</sup>; (f) -NH-CO-R<sup>7</sup>; (g) -NR<sup>8</sup>R<sup>9</sup>; (h) -SOR<sup>11</sup>, worin R<sup>11</sup> C<sub>1-6</sub>-Alkyl oder C<sub>1-4</sub>-Perfluoralkyl ist; (i) -SO<sub>2</sub>R<sup>13</sup>, worin R<sup>13</sup> C<sub>1-6</sub>-Alkyl oder C<sub>1-4</sub>-Perfluoralkyl ist; (j) -O-CO-R<sup>14</sup>, worin R<sup>14</sup> H, C<sub>1-6</sub>-Alkyl, Phenyl oder substituiertes Phenyl, wie hier definiert, ist; (k) O-CO-NR<sup>8</sup>R<sup>9</sup>; oder (1) -CN ist;

jedes  $R^{16}$ , unabhängig von den anderen, Wasserstoff;  $C_{1-6}$ -Alkyl; Benzyl;  $(C_{1-6}$ -Acyloxy)- $(C_{1-6}$ -alkyl) oder  $C_{1-4}$ -Perfluoralkyl ist;

T Wasserstoff oder - $OR_{15}$  ist, worin  $R_{15}$  Wasserstoff,  $C_{1-6}$ -Alkyl,  $(C_{1-6}$ -Alkyl)acyl, Phenylacyl, substituiertes Phenylacyl, wie hier definiert, Benzoyl oder substituiertes Benzoyl, wie hier definiert, ist; und die anderen Variablen wie in Anspruch 3 definiert sind.

5. Zusammensetzung nach Anspruch 1, worin in der Formel X O oder S ist;
R¹ Wasserstoff, C<sub>1-4</sub>-Alkyl, C<sub>1-4</sub>-Alkylacyl, -(CH<sub>2</sub>)<sub>p</sub>OR<sup>a</sup>, worin R<sup>a</sup> C<sub>1-4</sub>-Alkyl oder Phenyl ist und p 1, 2 oder 3 ist, (C<sub>1-4</sub>-Acyloxy)-(C<sub>1-4</sub>-alkyl), (C<sub>1-4</sub>-Alkoxy)carbonyl oder (C<sub>1-4</sub>-Acyloxy)-(C<sub>1-4</sub>-alkoxy)-

oder 3 ist,  $(C_{1-4}$ -Acyloxy)- $(C_{1-4}$ -alkyl),  $(C_{1-4}$ -Alkoxy)carbonyl oder  $(C_{1-4}$ -Acyloxy)- $(C_{1-4}$ -alkoxy)-carbonyl ist; jedes von  $\mathbb{R}^2$ ,  $\mathbb{R}^3$ ,  $\mathbb{R}^4$  und  $\mathbb{R}^5$  unabhängig von den anderen Wasserstoff, Halogen, Hydroxyl;  $C_{1-3}$ -Alkyl;

jedes von  $R^2$ ,  $R^3$ ,  $R^4$  und  $R^5$  unabhängig von den anderen Wasserstoff, Halogen, Hydroxyl;  $C_{1-3}$ -Alkyl;  $C_{1-3}$ -Alkylthio;  $C_{1-5}$ -Acyloxy; Benzoyloxy;  $C_{1-3}$ -Trihalogenalkyl;  $C_{1-4}$ -Aminoalkyl;  $C_{1-5}$ -Acyl;  $(CH_2)_mCOOR^6$ , worin m 0, 1, 2, 3 oder 4 ist und  $R^6$  H, Phenyl oder  $C_{1-6}$ -Alkyl ist; oder  $(C_{1-4}$ -Acyloxy)- $(C_{1-4}$ -alkoxy)carbonyl ist; und

T wie in Anspruch 1 definiert ist.

6. Zusammensetzung nach Anspruch 1, worin die Verbindungen der Formel I durch die Formel III wiedergegeben sind: worin

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- $R^1$  H,  $C_{1-4}$ -Acyl,  $(C_{1-4}$ -Acyloxy)- $(C_{1-4}$ -alkyl) oder  $(C_{1-4}$ -Acyloxy)- $(C_{1-4}$ -alkoxy)carbonyl ist;
- R<sup>2</sup> Halogen ist;

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- R<sup>3</sup> OH, C<sub>1-5</sub>-Acyloxy, Benzoyloxy oder (C<sub>1-4</sub>-Acyloxy)-(C<sub>1-4</sub>-alkoxy)carbonyloxy ist;
- R <sup>4</sup> H, OH, C<sub>1-4</sub>-Alkoxy oder C<sub>1-4</sub>-Acyloxy ist und entweder in der Stellung 1 oder der Stellung 2 angeordnet ist;
- R<sup>5</sup> OH, C<sub>1-4</sub>-Alkoxy oder C<sub>1-4</sub>-Acyloxy ist;
- T Wasserstoff oder C<sub>1-4</sub>-Alkoxy ist;

oder pharmazeutisch annehmbare Salze solcher Verbindungen sind.

7. Zusammensetzung nach Anspruch 1, worin in der Formel die Variablen wie in nachstehender Tabelle angegeben sind:

	Verbindung	X	<u>R</u> 1	R <sup>Z</sup>	R <sup>3</sup>	_R <sup>4</sup>	<u>R</u> 5	Ţ
15								
	1	S	н	H	Н	Н	н	н
	2	S	Мe	2-t-8u	1-L-8u	H	Н	1- <b>0</b> H
20	3	S	He	2-t-8u	4t-8u	H	н	1-CHe
	4	5	Me	2-1-80	4-t-8u	H	H	1-OAc
	5	S	Ac	2-t-8u	4_t-8u	н	н	1OH
25	8	S	н	2-t-8u	4-1-8u	н	н	1-CHe
	7	\$	н	2-t-8u	4 t-8u	H	н .	1-0Ac
	8	٥	н	2-t-Bu	4 t-8u	H	H	1- <b>CH</b>
	9	S	CH <sup>2</sup> OVC	2-t-Bu	4-t-8u	H	н	1- <b>OH</b>
30	10	S	н	1-01	11	11	il	3-OH
	11	S	Н	1-01	11	11	11	3-OAc
	12	S	н	1-01	11	11	H	3-OMe
35	13	5	Мe	1-C1	н	H	H	3-OH
	14	S	Не	1-01	H	н	H	3-OAc
	15	S	Жe	1-01	н	H	н	3-0%e
40	16	S	CH <sup>2</sup> OAc	1-C1	н	н	н	3-CMe
- <del></del>	17	<b>S</b> .	CH <sup>2</sup> DAc	1-01	н	н	н	3-QAC
	18	0	н	1-01	н	H	11	3- <b>0</b> H
	19	0	ře	1-01	н	H	H	3-OH
45	50	0	ře.	1-C1	н	H	н	3-0Ac
	21	0	Ne	1-01	Ħ	H	н	3-OMe

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	Verbindung	<u> </u>	<u>R</u> 1	<u>R</u> 2	R <sup>3</sup>	_R <sup>4</sup>	RS	Ţ
5	22	0	Ac	1-01	H	Н	н	3-0Ac
	23	0	CH <sub>2</sub> OAc	1-01	H	Н	H	3-0 <del>11e</del>
	24	Se	Me	1-C1	H	H	H	3-0 <b>%e</b>
10	25	\$0	н	1-01	11	н	11	3OH
,,	26	SO	н	1-C1	11	В	ŧŧ	3-0 <b>%e</b>
	21	SO	Н	1-01	11	H	11	3-0Ac
	28	SO	Me	1-C1	н	Ĥ.	н	3-0H
15	29	so	Me	1 C1	н	н	11	3 DAC
	30	SO	Me	1-01	н	Ħ,	н	3-0He
	31	so <sub>2</sub>	ĸ	1-01	н	H	н	3-OH
20	32	20 <sub>2</sub>	н	1-C1	11	H	11	3-QAc
	33	so <sub>2</sub>	н	1-01	H	н	н	3-Che
•	34	so <sub>2</sub>	Me	1-01	н	н	н	3-0Ac
25	35	s0 <sub>2</sub>	Нe	1-01	7-00H <sub>2</sub> 00 <sub>2</sub> H	Н	Я	3-CAc
20	36	so <sub>2</sub>	Нe	1 01	н	н	н	3 0Me
	31	so <sub>2</sub>	Ac	1_01	н	н	H	3-OH
	38	۶0 <sub>2</sub>	Ac	1-C1	н	н	H	3-CAC
30	39	so,	Ac	1-01	н	н	н	3-0%e
	40	so	Ac	1-C1	н	H	н	3-OH
	41	SO	Ac	1-C1	H	н	н	3-0Ac
35	42	SD	Ac	1 01	н	н	н	3 -0%
	43	50 <sub>2</sub>	CH <sub>2</sub> OA¢	1-C1	н	H	н	3-OH
	44	SO <sup>5</sup>	CH20Ac		н	H	н	3-OAc
10	45	soz	CH <sub>2</sub> CAc		н	н	н	3-0Me
40	46	5	CH <sub>2</sub> Ph	11	П	П	11	н
	47	5	ñe .	н	u	н	H	11

	Verbindung	<u>x</u>	<u>R</u> 1	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	<sub>R</sub> 5	Ţ
								-
5	48	\$	Ac	н	н	н	Н	н
•	49	s	CHZOAC	н	н	н	н	н
	50	0	н	н	H	Н	н	H
	51	0	Me	н	н	н	11	11
10	52	0	Ac	н	H	Н	11	н
	53	Se	н	н	н	11	н	11
	54	Se	Ме	н	н	н	Ħ	H
15	55	Se	Ac	H	H	Н	Н	H
	56	Se	CH_OAc.	н	н	Н	н	Н
	57	so	н	н	н	11	11	11
20	58	SO	Ke	H	н	н	н	11
	59	so <sub>2</sub>	Ac	н	н	н	H	н
	60	s	н	H	н	H	Н	3- <b>0</b> H
	61	\$	н	н	н	н	H	3-0Ac
25	62	S	н	H	н	н	H	3-CMe
	63	S	Жe	H	Н	H	11	3-0Ac
	64	S	Нe	H	н	11	H	3-CH
30	65	S	Жe	Н	II	Ħ	11	3-0he
	6 <b>6</b>	S	Ac	H	н	H	11	2- <b>C</b> H
	67	S	Ac	Н	н	H	Ħ	3-0Ac
35	68	S	Ac Ac	H	н	н	15	30Me
	69	S	CH <sub>2</sub> OAc	н	Н	H	Н	3-CH
	70	S	CH2OAC	н	H	Н	H	3-0Ac
	71	\$	CH <sub>2</sub> OAc	H	11	Н	H	3-0Me
40	72	wie V	erbindu	ıngen	60-71	, jedo	ch X=	=0
	73	wie V	Verbind	ungen	60-71	, jed	och X	=Se
	74	\$	н	4-C1	н	Н	Н	3-OH
45	75	\$	H	4C1	Ħ	H	H	3-0Me
	76	5	Н	4-C1	H	н	Н	3-0Ac

	Verbin	duna	X	<u>R</u> 1	R <sup>2</sup>	<u>R</u> 3	R4	R <sup>5</sup>	T	
	VCIDII				_					
	;	17	\$	He	4-C1	H	H	н	3-OH	
5		78	s	Me	4C1	H	H	н ,	3-0Ac	
	S	19	\$	He	4-C1	н	H	Н	3-0 <del>11</del> e	
		80	S	Ac	4-C1	н	н	н	3-0H	
10	:	81	S	Ac	4-C1	н	н	H	3- <b>0</b> Ac	
		82	S	Ac	4-C1	н	Н	H	3- <b>0</b> 4e	
		83	s	Me	4_C1	H	H	н	3-0-8z	
15		84	S	Me	4-C1	н	Н		COCH(Me) <sub>2</sub>	
		85	\$	He	4_C1	н	H	н 3-с	COC (%e) 3	
		86	so <sub>2</sub>	н	4-C1	H	u	11	3-04	
		87	so <sub>z</sub>	н	4-0H	11	11	11	3-CH.	
20		88	so <sub>2</sub>	я	4-C1	н	H	11	3-CAc	
	15	89	50 <sub>2</sub>	н	4-C1	н	н	H	3-0Me	
		90	so <sub>2</sub>	Me	4-C1	н	н	н	3-OH	
25		91	so <sub>2</sub>	Нe	4-C1	н	н	Н	3-CAc	
		92	50 <sub>2</sub>	#e	4-C1	н	н	н	3-0 <del>1/e</del>	
		93	so <sub>2</sub>	Ac	<b>4</b> _C1	н	H	H	3-OH	
30	20	94	50 <sub>2</sub>	Ac	4-C1	н	н	Ħ	3-CAC	
		95	so <sub>2</sub>	Ac	4 C1	н	н	Ħ	3-CHe	
		96	s	CH <sub>2</sub> OAc	4 C)	H	н	н	H	
		97	S	CHZCAC	4-01	H	н	Ħ	3-OH	
35		98	s	CH <sub>2</sub> OAc		н	н	Н	3-0Ac	
	25	99	s	CH <sub>2</sub> CAc	4-C1	н	Я	н	3-0#e	
		100	so <sub>2</sub>	CH <sup>2</sup> OAc	4-C1	н	н	н	3 OH	
40		101	so <sub>2</sub>	CHZOAc	4_¢1	H	н	н	3-QAC	
		102	so <sub>2</sub>	CH <sub>2</sub> CAc		H	H	ii	3-0Me	
		103	-	Verbind	lungen	74-	-103,	jedoch	X=SO	
45	30	104	wie	Verbind	lungen	74-	-103,	jedoch	X=O	
•		105	wie	Verbino	dungen	74-	-103,	jedoch	ist R <sub>4</sub>	7-C1

	Verbindung	χ	<u>R</u> 1	R <sup>2</sup>	R <sup>3</sup>	_R <sup>4</sup>	R <sup>S</sup>	<u> </u>	
						•			
5	106	wie	Verbind	lung 10	5, je	doch	X=O		
	107	wie	Verbind	lungen	74-10	3, je	edoch	ist R <sub>4</sub>	7-0Me
	108	wie	Verbind	lung 10	7, je	doch	X=O	_	
	109	wie	Verbind	lungen	74-10	3, j∈	edoch	ist R <sub>4</sub>	7-C <sub>1-6</sub> -Alkyl
10	110	wie	Verbind	lung 10	9, je	doch	X=O		
	111	wie	Verbind	lunge 7	4-103	, jed	loch i	st R <sub>4</sub> 7	-COMe
	112	wie	Verbind	lung 11	1, je	loch	X=O		
15	113	wie	Verbind	lungen	74-10	3, je	edoch	ist R <sub>4</sub>	7-CH <sub>2m</sub> COOR,
		WOT	in m 0 k	ois 4 i	st				
	114		Verbind						
	115	wie	Verbind					ist R <sub>4</sub>	9-C1
20	116	S	Н	4-Et	H	H 	H		
	117	S	Me	4-Et		H		3-GAc	
	118	S	He	4-E <b>t</b>		н	H		
25	119	S	Me	4-Et	Н	H	K	30Me 30H	
	120	S	н	4-0Et	H	н.	H		
	121	\$	н	4-0E t	H	<b>н</b> 	н и	3-CMe 3-CMe	
	122	\$	Жe	4-0E t	H	н	н "	3-0Ac	
30	123	S	Me	4-0Et	Н	н 	Н	3-OH	
	124	\$	н	2-0Et	7-0Et	H	H	3-0He	
	125	S	H	2-0Et	7-0Et	H	H	3-0Me	
35	126	S	Me	2-0E1			н	3-0Ac	
	127	\$	Ke	2-0Et	7-0Et	H	н	3-OAC	
	128	S	H	н	H	и	3-Ac	н	
40	129	s	Me	н	H	H	3-Ac	3-0Ac	
40	130	\$	<b>Ac</b> 	H 7 4-	H	H	3-Ac	н	
	131	\$	Н	7-Ac	H H	и.	3-Ac	н	
	132	<b>S</b>	Me	1_Ac 7_Ac	н	н	3-Ac	н ·	
45	133	2	Ac	1-46	77	••			

	Verbi	ndung	x	<u>R</u> 1	R <sup>2</sup>	<u>R</u> 3	<u>R</u> 4	R <sup>S</sup>	Γ
	<u></u>								
5		134	S	CH <sub>2</sub> OAc	7-Ac	Н	Н	3-Ac	Н
		135	\$	н	2- <b>4e</b>	4-C1	н	H	3-OH
	5	136	\$	Жe	2- <b>He</b>	4-C1	н	Н	3-0Ac
40		137	S	H	7-Me	2-He	н	H	3-OH
10		138	\$	ře	7-He	2-He	н	Н	3-OAc
		139	\$	н	2-0Et	4-C1	н	H	3-OH
		140	\$	Me	2-0Et	4-C1	н	H	3-OAc
15	10	141	\$	н	2-5-n-8u	4-C1	н	н	3-OH
		142	\$	He	2-5-n-84	4C1	н	н	3QAC
		143	S	Нe	4-5-n-8u	н	H	н	3-OAC
20		144	S	Me	2-0-Ne	4-8r	H	н	3-0Ac
		145	S	ñe	2-0-#e	4-C1	н	H	3-OAc
	15	146	\$	ře	2-0-He	4-8r	н	H	3-OH
		147	\$	н	2-0-He	3-OH	н	н	7-OHe
25		148	\$	н	1-CHe	3-OH	н	Н	7-Che
		149	S	H	2-CMc	3-OH	1-8r	H	7 -CMc
		150	\$	н	1-CHe	3-OH	2-8r	H	7-CMe
30	20	151	\$	н	1-OHe	3-OH	4-8r	н	7 -0Me
		152	s	н	1-CHe	3-OH	2-01	н	7-CHe
		153	S	н	1-CMe	3- <b>O</b> H	4_C1	H	7- <b>0%e</b>
35		154	S	н	2-0Me	3-OH	1-C1	н	7-Offe
		155	S	н	2-0 <del>1/e</del>	3-OH	4_01	н	7 -CMe
	25	156	\$	н	2-0Et	3-OH	1-8r	н	7-0EŁ
		157	5	н	2-0£t	3OH	4-Br	н	7-0€ t
40		158	S	н	2-0£t	3-OH	1'-c1.	н	7-0EL
		159	S	H	2-06 t	3-OH	4_C1	H	7-0Et
	-	160	S	н	2-CMe	3-OH	1-8r	7-08	
45	30	161	S	H	2-CHe	3-OH	4-Br	7-04	e 8-0 <del>ne</del>

	Verbindung	x	R1	<u>R</u> 2	<sub>R</sub> 3	<u>R</u> 4	_R <sup>S</sup>	<u> </u>
5	162	S	н	2-CMe	3-OH	4-F	н	7-0Me
•	163	S	н	2-0Me	3-0H	4-CF <sub>3</sub>	H	7-CMe
	164	5	н	2-CHe	3-OH	4Br	н	1-0Et
	165	\$	н	2-CMe	3-CH	4-C1	H	7-06 t
10	166	\$	H	2-QHe	3-CH	4-F	н	7-0Et
	167	S	н	2-OHe	3-OH	<b>4</b> _I	H	7-CMe
	168	S	H	2-CMe	3-OH	4-CF <sub>3</sub>	н	7-0Et
15	169	5	н	2-0Et	3 <b>–</b> 0H	4-Br	H	7-0Me
	170	5	н	2-0É t	3-OH	4-C1	н	7-CMe
	171	\$	н	2-0Et	3-OH	<b>4</b> F	н	7-0He
20	172	S	н	2-0Et	3OH	4-CF <sub>3</sub>	Н	1-0Me
	173	S	н	1-CMe	2-CHe	3-CH	4-8r	1-CMe
	174	S	н	)-Otte	3-OH	H	н	2-0 <b>Me</b>
	175	S	н	1-0He	3-OH	48r	H	2-CMe
25	176	wie	Verbin	dungen	147-1	.75, j	edoch	. X≃O
	177	wie	Verbin	dungen	147-1	75, je	edoch	_
	178	\$	H	2-SMe	3- <b>CH</b>	4-8r	н	7-One
30	179	S	н	2- <b>0He</b>	3-CH	4-8r	7-5He	
	180	502	н		e 3-OH		н	7 <b>-</b> 0 <b>ne</b>
	181	wie	Verbino	lungen	147-1	75, je	edoch	X=SO
35	182	S	H	4C1	Н	Н	Н	3-08z
	183	S	Н	4c1	Н	Н	н з-	00001(Ne) <sub>2</sub>
	184	\$	Ac	н	H	7 <b>-</b> F	Ħ	3-OAc
	185	S	Мe	н	н	7-He	H	3-CMe
40	186	S	н	н	11	7-F	11	3-0Ac
	187	\$	He	H	, <b>H</b>	9 <b>-</b> C1	Н	3-CMe
	188	\$	<del>Ke</del>	н	Н	9-C1	Н	3-0Ac
45	189	\$	ře	H	Н	7-4e	н	3-0/c

	Verbindung	X	1 1	2	R <sup>3</sup>	R <sup>4</sup>	<u>R</u> S	
					-			• •
5	190	S	н	Н	11	9-C1	Н	3-OAC
	191	S	н	н	4-CF <sub>3</sub>	H	Ħ	3 QAC
	192	S	н	н	4C1	н	н	3-01s
10	193	S	Ac	н	4-C1	7 <i>-</i> F	H	3-OMe
	194	S	Ac	H	4-C1	7_F	Н	3-OH
	195	2	Me	н	4-C1	7 <b>-</b> F	Н	3-OHe
	196	so	Н	н	н	н	11	3 CAC
15	197	so <sub>2</sub>	н	н	н	н	H	3 CAC
	198	so <sub>2</sub>	н	н	н	H	11	3 CH
	199	so <sub>2</sub>	н	н	H	7-F	H	3-OAC
20	200	so <sub>2</sub>	н	н	4-C1	H	Н	210 <del>-</del> E
	201	s	н	1-04e	2-OMe	4-Me	н	3 -OH
	202	S	H	1-Che	2-CMe	4- <b>He</b>	H	3-OAc
25	503	205	н	1-CMe	2-CMe	4_He	H	3-QH
	204	so <sub>2</sub>	H	4-0Mc	н	н	н	3 CH
	205	\$	н	2-OMe	3-OH	4-8r	7-CHe	н
	206	S	н	2-CMe	3-0Ac	4_8r	7-CHe	H
30	207	S	н	2-CMe	3-OAc	4-C1	7-04e	н
	208	50 <sub>2</sub>	н	2-CHe	3-OH	4-8r	7-che	н
	209	s	н	Z-OMe	3-OAc	7-C#e	4-8r	H
35	210	S	H	2-CHe	3-0Ac	7-0He	4-Br	H
	211	5	н	2 -CMe	3-OBz	7-CHe	4-8r	H
	212	\$	Ne	2-CMe	3-0 <b>%</b> e	7-CHe	4-8r	н
40	213	\$	н	2-CMe	3-0Mc	7-CMe	4-86	н
	214	S	Ac	2-CMc	3-CAc	7-CHe	4-8r	н
	215	\$	Ac	2-OHe	3-OH	7-C4e	4-8r	н
	2:6	s	Ac	2-CHe	3 <b>-</b> 0#e	1-04e	4-85	н
45	217	\$	Нe	2-04e	3-0Ac	7-04e	4-3r	н

	Verbindung	<u>x</u>	<u>R</u> 1 R	²	R <sup>3</sup> R	4	<u>R</u> S	
				•				
5	218	\$	He	2-04		7-0 <del>1/e</del>	4-8r	н
	219	s0 <sub>2</sub>	н	2-Cre	3-OH	7-CMe	4—Br	H
	220	502	н	2-0 <del>14e</del>	3-0Ac	7-0 <del>1/e</del>	4 <u>-</u> 8r	H
10	221	so <sub>2</sub>	н	2-CMe	3-0Ac	1-CMe	4-Br	н
	222	SO	H	2-CMe	3-0Ac	7-0 <del>11e</del>	4-8r	н
	223	SO	H	2-C4e	3-0Ac	7-0 <del>1/e</del>	4-8r	н
	224	\$	н	2-Cre	3-000 <sub>2</sub> re	4-8r	7-C <del>Me</del>	н .
15	225	s	н		3-000 <sub>2</sub> Et	4-8r	7-OMe	н
	226	S	н		3-000,0H(Ne)0Ac	4-8r	7-0He	H
	227	\$	н		3-000 <sub>2</sub> 0H(Me)0Ac	4C1	7-04e	н
20	2 <i>2</i> 8	s	∞್ನ∺∈	2-04e	-	4-8r	7-Ore	н
	229	\$	α, ει	2-CHe	3-CH	4-81	7-CMe	H
	230	S	ω <sub>2</sub> αι(‰)ολο	2-CHe	3-CH	4-8r	7-CHe	н
25	231	5	ದ್ದಾರಃ(೫೬)ಯ		3-CH	4-C1	7-OMe	н
20	232	S	ක <sub>2</sub> CH(%e)0Ac			<b>4</b> -F	7-0%e	н
	233	s	ದ್ದಾರ⊦(№)೦೩೯	2-Ore	3-OAc	4-8r	7-0 <del>1</del>	н
	234	\$	∞ ූටi(re)OAc		3-000 <sub>2</sub> CH(He) DAc	4-Br	7-0Me	н
30	235	0	Ac	2-CHe	<del>-</del>	4_8r	7-0 <del>14e</del>	н
	236	0	Ac	2-Cre	3-QAc	4-ar	7-0 <del>4e</del>	н
	237	0	ಹೄರಗ(೫e)0Ac	2-0%e	3-OH	4-8r	7-0Me	н
35	238	0	യുവ(Ne)OAc		3-0Ac	4-8r	7-OHe	н
	239	\$	н	2-OHe	3-CH	4-Br	7-Me	н
	240	S	H	2-0 <del>11e</del>	3-QAC	4-8r	7-Me	H
	241	s	н	2-CMe	3-CH	4-8r	7-F	н
40	2 <b>42</b>	\$	Я	2-CHe	3-0/4	1-8r	7-F	н

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	Verbindung	<u>x</u>	R1_	Ŗ <sup>2</sup> _	R3_	Ŗ <u>.</u>	<u>R</u> 5	ī
			u	н	H	н	н	occet
5	243	S	H		3-C1	H	н	000-n-Pr
	2 <b>44</b>	S	H	2_01			н	000-n-8u
	245	\$	<b>H</b>	Н	4-C1	H		н
40	246	\$	H	1-Me	H	H	н	н
10	247	\$	Н	2-CF <sub>3</sub>	H	Н	H	
	248	S	H	2-Et	н	H	н	H
	249	S	Η·	н	3-C1	7-CMe	H	н
15	250	\$	н	H	3-C1		Н	Н
	251	S	Н	н	3-NO <sub>2</sub>	н	7-NO <sub>2</sub>	н
	252	\$	н	3-NMe_2	н	и.	7-KMe2	H
20	253	S	н	1-0H	н	я	н	н
ZŲ	254	\$	н	3-0Ac	7 .F	н	н	H
	255	\$	н	3-CH_CDMe	4-C1	н	н	Н
	256	5	н	3-0000HHe <sup>5</sup>		4-C1	н	н
25	257	S	Ac	3-CMe	401	H	н .	н
	258	0	H	2-CF <sub>3</sub>	H	н	H	н
	259	S	Me	н	3-OMe	н	4-C1	Н
30	260	502	н	4-C1	3-04	Н	н	н
	261	\$	Xe	7 <i>-</i> F	4_C1	3-CHe	н	н
	262	\$	Me	3-0Me	1-ne	н	н	H
35	263	S	Ac	4-C1	Н	н	Н	Н
35	264	S	Ac	3-OAc	4-¢1	н	H	H
	265	502	Ac	4-C1	H	н	н	3-OH
	266	205	Ac	4-C1	H	н	H	3-OAc
40	267	so <sup>5</sup>	Αç	4-8r	н	Н	H	3-GAc

	Verbindung	Ā	RI.	¥2_	<u> 8</u> _	<u>R</u> 4_	<u> </u>	Ţ
6	268	so <sub>z</sub>	CO CH (Me) OAC	4-C1	н	н	Н	3-OH
	<b>269</b>	SO <sup>2</sup>	н	4 <b>-</b> C1	н	н 3-00	D <sup>C</sup> CH(We)OAc	Н
10	270	0	Ac	4-C1	н	11	11	3-0AC
15	271	0	CO2 CH (Me) CAC	4-C1	н	н	н	3-OH
	212	0	<b>ග</b> ුශ(№)0Ac	4 -C1	H	<b>H</b>	н	2-0Ac
20							•.	
	273	0	н	4_C1	н	II 3-00	0 <sub>2</sub> CH(Ne)OAc	н
25	274	S	CH <sub>2</sub> OAc	4-C1	Н	н	н	3-OAc
	275	\$	CH(Ne)OAc	4-C1	н	н	н	3-0Ac
30	276	s	н	2-Crie	3-011	7-ОН	н	,,
	277	s	н .	2-0 <del>11e</del>	3-OH	7-OH .	4-8r	н
35	278	\$	н	2-CHe	3-0Ac	1-он	4-8r.	н
40	279	5	н	2-CHe	3-0Ac	7-0Ac	4-8r	н

	Verbindung	<u>x</u>	<u>R</u> 1	<u>R</u> 2_	<u>R</u> 3	<u>R</u> 4	<u>8</u> 5_	Ţ
5	280	s	Ac	2 -CMe	3-0H	1-0H	4~Br	н
	281	\$	Ac	2-OMe	3-0Ac	7-CH	4-8r	H
	282	\$	Ac	2 -OMe	3-0Ac	7-0Ac	4-Br	H
10	283	s	Ac	2-0Me	3-OH	7-QAc	4-8r	н
70	284	so <sub>2</sub>	Ac	2 -OMe	3-OH	4-Br	7-0Me	н
	285	so <sub>2</sub>	CD_CH(Me) QAc	2-0 <del>11e</del>	3-0Ac	4-8r	7-CMe	н
15	286	so <sub>z</sub>	Ac	2CHe	H 1 3-000 <sub>2</sub> 00Ac 21 He	4-8r	7-0Me	н
20	287	so <sub>z</sub>	Ac	2-CMe	3-0Ac	4-8r	7-CMe	н
25	288	so <sub>2</sub>	CO <sub>2</sub> CH (Me) OAc	2-0Me	3OH	4-8r	7-0He	н
	289	s	Ac	2-0Et	3-0Ac	4-C1	н	н
	290	S	Ac	2-0Et	3-OH	4-C1	н	н
30		S	Me	н	1-Ac	н	н	3-CMe
	292	S	Me	н	н	7-F	н	3-0Me
	293	S	Ac	н	н	7-F	н	3-0Me
35	204	\$	Ac	н	н	1-F	н	3-OH

- 8. Zusammensetzung nach Anspruch 7, worin die Verbindung eine der mit 13, 14, 31, 37, 38, 73, 76, 78, 79, 80, 81, 82, 84, 86, 87, 88, 92, 93, 94, 124, 139, 147, 151, 153, 155, 157, 159, 162, 163, 164, 165, 169, 170, 178, 179, 182 bis 223 einschließlich, 225 bis 242 einschließlich, 260 oder 267 bis 294 einschließlich numerierten Formeln hat.
- Zusammensetzung nach Anspruch 7, worin die Verbindung eine der mit 79, 80, 81, 86, 88, 93, 94, 197, 198, 214, 215, 226, 230, 233, 235, 236, 237, 275, 280, 283, 284, 287, 288, 289 und 290 numerierten
   Formeln hat.
- Zusammensetzung nach Anspruch 1 zur Verwendung bei der (a) Inhibierung der Leukotrien-Biosynthese oder -wirkung in Säugetieren; (b) Behandlung von Herz-Kreislauf-Zuständen; (c) Behandlung von Entzündungen; (d) Behandlung von Allergien; (e) Behandlung von Schmerz; (f) Behandlung von Asthma; oder (g) Behandlung von Hautzuständen.
  - 11. Verbindungen der Formel:

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worin die Substituenten wie in der nachstehenden Tabelle angegeben sind:

15	Verbindung	Ī	<u>R</u> 1	R <sup>2</sup> _	<u>R</u> 3_	<u>R</u> 4_	<u>8</u> 5_	. I
	3	\$	Me	4-C1	н	н	н	3-CMe
	8	S	Ac	4-C1	н	н	н	3-0Ac
20	9	S	Ac	4 <b>-</b> C1	н	н	H	3 <i>-</i> CH
25	Verbindung	Ā	<u>R</u> 1_	<u>R</u> 2	<u>R</u> 3_	<u>R</u> 4	<u>R</u> S_	<u>1</u>
	21	\$	Ac	н	4-01	1-F	н	3-0 <b>%e</b>
30	28	\$	Ac	н	4-C1	1-5	н	3-CH
	29	\$	He	н	4-C1	7-4	н	3-OMe
	30	\$	н	н	2-0Et	4-C1	H	3-OH
35	32	so <sub>2</sub>	н	н	н	н	н	3-0Ac
	33	ໝູ້	н	н	4-C1	H	н	3-0Ac
	34	so <sub>2</sub>	H	н	4-C1	н	н	3-OH
40	39	s	н	1-0He	2-0 <del>14e</del>	4 <b>-%e</b>	н	3-OH
-	40	\$	н	1-0Me	2-0He	4He	н	3-0Ac
	41	502	н	1-0%e	2-0 <del>11e</del>	4 <b>-∺e</b>	Ħ	3-0H

	Verbindu	ing :	<u>x</u>	<u>R</u> 1_	<u>R</u> 2_	<u>R</u> 3_	<u>R</u> 4	<u>R</u> 5_	Ī
5	43	1	\$	н	1-OH	2-C(He) <sub>3</sub>	н 4-с	(Fe) <sub>3</sub>	н
	49	)	SO	н	1-0He	2-014e	4-14-	н	3-OH
	so	) :	50	н	1-GHe	2-0Me	4-He	н	3-CAc
10	51		so <sub>2</sub>	н	1-0He	2-Offe	4-He	н	3-0Ac
	S2	:	s	н	2-0 <del>1'e</del>	3-OH	4-8r	7-0%e	н
	\$3	;	s	н	2-0He	3-OH	4C1	7-0Me	Н
15	54	. !	\$	н	2-0 <del>1/e</del>	3-0Ac	4—8r	7-0 <b>%</b>	н
	55	:	s	н	2-0Me	3-0Ac	4C1	7-0%e	Н
	56	. !	so <sub>2</sub>	н	2-CMe	3-OH	4 <del>-</del> 8r	7-Offe	Н
20	\$8	;		н	2-0 <del>1/e</del>	3-OAc	4 <u>–</u> 8r	7-0Me	Н
	59			Ac	Z-OMe	3-OH	4-8r	7-CMe	н
	60	) (	0	Aç	Z-CHe	3-Q4¢	4—8r	7-OMe	н
05	61	(	مره ه	H(%e)OAc	2- <b>0%</b> e	3- <b>0</b> H	<b>4</b> -8r	7-OMe	н
25	62			H(Me)OAc		3-OAc	4 <u>-</u> 8r	7- <b>OMe</b>	н
	63		-	н	2-0 <del>1/e</del>	3-OH	48r	7- <b>Xe</b>	н
	64	:	S	н	2-0 <b>%</b> e	3-OAc	4-8r	7 <b>-Xe</b>	н
30	65	;	S	н	2-CMe	3-CH	48r	7-F	н
	66		S	н	2-0Me	3-0Ac	4-8r	7 <b>-</b> F	н
	67	7	so	н	2-CMe	3-OAc	4-8r	7-0Me	н
35	88	3	so <sub>2</sub>	н	2-OMe	3-OH	н	7-0 <b>%</b> e	H
	69	) :		н	2-CHe	3-0Ac	н	7-0Me	H
	70			Aç	2-0 <del>1/e</del>	4-8r	7-Offe	H	3-QAc

	Verbindung	x	<u>R</u> 1_	<u>R</u> 2	<u>8</u>	<u>R</u> _	ë.	Ī
5	71	5	Ac	2-CHe	4-C1	7-OHe	н	3-0Ac
	12	5	Ac	2-OMe	4_F	7-0He	н	3-0Ac
	73	\$	Ac	2-CHe	4-1	7-CMe	н	3-0Ac
10	74	5	Ac	2-GMe	4-CF <sub>3</sub>	7-0Me	H	3-QAC
	15	5	Ac	2-CHe	4-CH	7-0Me	н	3-0Ac
	76	S	Ac	2-0EL	4-8r	7-0Et	н	3-0Ac
	17	5	Ac	2-0Et	4-C1	7-0Et	н	3-0Ac
15	78	S	Ac	2-011e	4-8r	7-0Et	н	3-0Ac
	79	\$	Ac	2-CMe	4-C1	7-0£t	н	3-0Ac
	80	5	Ac	2-CNe	4 <b>-</b> F	7-0Et	H	3-QAc
20	81	\$	Ac	2-0Et	4-8r	1_CMe	н	3-CAc
	82	\$	Ac	2-0Et	4-C1	7-CMe	н	3-0Ac
	83	\$	Ac	2-0Et	4_F	7-OHe	н	3-0Ac
25	84	\$	Ac	2-0Et	4-CF <sub>3</sub>	7-0Me	н	3-QAc
	85	S	н	2-CMe	4-8r	7-CHe	н	3-OH
	86	\$	н	2-CMe	4-C1	7-CMe	H	3-OH
	87	\$	н	2-CHe	4_F	7-0Me		3-0H
30	88	\$	н	2-CMe	4-CF <sub>3</sub>	7OMe	н	3-OH
	89	\$	н	2-CMe	4 <i>-</i> 8r	7-CMe	н	3-OAC
	90	\$	н	2-CMe	4-Br			3-OBZ
35	91	\$	н .	2-0Me				3-OCOCHMe <sup>2</sup>
	92	\$	н	2-CMe	4-Br		3-00H2002H	
	93	\$	Ac	2-CMe	4-8r	7-0Me	ĸ	3-08z
40	94	5	Ac	2-CHe	4-Br	7-CMe	н	3-CMe
	95	S	AC	2 <del>-</del> 0% <del>e</del>	4-8r		3_0C+2CD2H	
	36		Ac				3-0CH2CD2H	
45	91	\$	CH <sub>2</sub> CAc	2-CHe	4-8r			3-OH
40	98	3	CH <sup>2</sup> 0yc					3 -CH
	99	S	CH <sup>2</sup> 0yc	2-CMe	4-8r	7 –C.He	н	3-0Ac

	Verbindung	Ā	<u>R</u> 1	<u>R</u> 2_	<u>R</u> 3_	<u>R</u> 4_	<u>R</u> 5_	Ī
5	100	5	CH <sub>2</sub> OAc	2-OMe	4-8r	7-0Me	н	3-08z
	101		CH <sub>2</sub> OAc		4-8r	1-OMe	н	3-0He
	102	S	сн <sub>3</sub>			7-0Me	н	3-OH
10	103			2-0Me		7-CMe	H	3-0Ac
70	104	\$	он <sub>3</sub>	2-0 <b>Me</b>	4-C1	7-0Me	н	3-OH
	105	S	He	2-0 <b>%e</b>	4 <b>_</b> F	7-0 <b>Me</b>	н	3-OH
	106	\$	Me	2-0 <b>He</b>	4-CF <sub>3</sub>	7-0He	н	3- <b>OH</b>
15	107	S	CH(Me)OAc	2-OMe	4-Br	7-OMe	н	3-OH
	108	s œ	i(Me)0C0C(Me) <sub>3</sub>	2-0Me	4-8r	7-04e	H	3-OH
	109	S	CH (Me) DAc			7-0Me		3-OH
20	110	S	CH (Me) DAc	2-0Me	4-F	7-0Me	H	3-OH
	111	\$	CH (Me) QAc	2-0Me	4-CF <sub>3</sub>	70Me	н	3OH
	112	\$	н	2-0Me	4-8r	7-0 <b>Me</b>	3-000 <sub>2</sub> Me	н
25	113	\$	н	2-0 <b>11e</b>	4-8r	7OMe	3-000 <sub>2</sub> Et	н
	114	S	H				3-000 <sup>2</sup> CH(Me)	
	115	5					3-000 <sub>2</sub> 01(Me)	
	116	\$	CO <sub>2</sub> Me	2-0 <b>%e</b>	4-8r	7-0He	н	3-OH
30	117	s	co <sup>S</sup> EF			7-0Me		3-OH
	118	\$	CD_CH(Me)OAc	2-OMe	4-Br	7-0Me	н	
	119	\$	CO_CH(He)OAc	2-OHe	4-C1	7-0He	H	
35	120	\$	CO2CH(He)OAc					3-OH
	121	\$	ක <sup>5</sup> cH (¥F) 0¥c					3-0Ac
	122	S	ಯ್ನರಗ(Me) OAc				3-000 <sub>2</sub> 0H(Me	
40	123	S	Ac '	2-OMe	4-Br	7-0He	H	3-OH
	124	S	Ac	2-0Me	4-C1	7-0 <b>Me</b>		3-OH
	125	\$	He	2-OMe		7-OMe		3-0 <b>He</b>
45	126	S	н	2-CHe	4-Br	7-OMe		30Me
40	127	\$		4-C1	н	H	<b>H</b>	3-QAc
	128	SO	2 Ac	4_C1	н	H	Н	3-OH

	Verbindung	<u>x</u>	<u>R</u> 1_	<u>e</u> 2_	<u>R</u> 3_	<u>R</u> 4_	<u>R</u> 5_	Ţ
5	129	so,	Ac	4-C1	• н	н	н	3-0Ac
	130	s	Ac	2-0Et	4-01	H	H	3-OH
	131	\$	Ac	2-0Et	4-C1	H	Н	3-0Ac
10	132	S	Aç	2-0 <b>%</b>	4-85	7-OH	н	3-OH
10	133	5	Ac	2-0Me	4 <u>-</u> 8r	7-QAC	H	3-OH
	134	so <sub>2</sub>	Ac	2-QMe	4-8r	1-0%e	H	3-CH
	135	\$0 <sub>2</sub>	Ac	2-04e	4-8r	1-0%e	н	3-0Ac
15	136	so <sub>z</sub>	ක <sub>2</sub> cH(№)0Ad	2-0 <del>1e</del>	4 <u>-</u> 8r	7-OMe	Н	3-OH
	137	\$	αΣ <mark>α ΙΟ (21</mark>	H	4-Br	7-OMe	Z-OMe	3OH
			Ne C(Me)	3				
20	138	\$	н	2-OMe	<b>4</b> -I	7-Offe	н	3-OH
	139	S	H	2- <b>0%e</b>	F-CX	7-0 <del>11e</del>	H ´	3- <b>CH</b>
	140	\$	H	2-0Et	4-8r	7-0Et	H	3-CH
25	141	S	н	2 <b>-0</b> Et	4 <b>-</b> C1	7-0Et	н	3-CH
	142	S	H	2-0He	48r	7-0Et	H	3-CH
	143	5	н	2-ONe	4-C1	7-0Et	H	3CH
30	144	\$	H	2-0 <b>He</b>	<b>L</b> _5	7-0Et	Ħ	3-OH
	145	\$	н	2-0Et	4_8r	7-OMe	Н	3-CH
	145	5	H	2-0Et	4-C1	7-OMe	н	3-OH
	147	\$	H	2-0Et	<b>4</b> F	7-Offe	H	3-QH
35	148	5	н	2-0Et	4-053	7-Offic	H	3-CH

- 40 12. Verbindungen mit Variablen in Formel I, in Anspruch 11 mit 3, 8, 9, 32, 33, 34, 41, 59, 60, 61, 70, 71, 114, 118, 119, 121, 123 oder 127 bis 137 einschließlich numeriert.
  - 13. Verbindungen mit Variablen in Formel I, in Anspruch 11 mit 70, 71, 118, 119, 121, 123 oder 137 numeriert.
  - 14. Verbindungen nach Anspruch 11 mit der Formel:

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worin die Substituenten wie in der nachstehenden Tabelle angegeben sind:

5	_R <sup>1</sup>	R <sup>2</sup>	_R <sup>3</sup>
	Н	Br	ОН
	н	Cl	ОН
10	н	F	ОН
	H	CF <sub>3</sub>	ОН
15	H	Br	OAc
	Н	Br	ocoph

	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
	Н	Br	OCOCHMe <sub>2</sub>
5	H	Br '	OCH2CO2H
	Ac	Br	OAc
	Ac	C1	OAc
10	Аc	Br	ocoph
,,	Ac	Br	OMe
	Ac	Br	OCH2CO2H
	Ac	Cl	och <sub>2</sub> co <sub>2</sub> h
15	CH <sub>2</sub> OAc	Br	OH
	CH <sub>2</sub> OAC	Cl	ОН
	CH <sub>2</sub> OAc	3r	OAC
20	CH <sub>2</sub> OAc	Br	ocoph
	CH <sub>2</sub> OAc	Br	OMe
	CH <sub>3</sub>	Вr	OH
	CH <sub>3</sub>	Br	OAC
25	CH <sup>3</sup>	Cl	ОН
	CH <sub>3</sub>	F	OH
	CH <sub>3</sub>	CF <sub>3</sub>	OH
30	CH (CH <sub>3</sub> ) DAG	Br	он
	сн (сн <sub>3</sub> ) осос (сн <sub>3</sub> ) <sub>3</sub>	Br	ОН
	CH (CH <sub>3</sub> ) OAc	Cl	ОН
35	CH (CH <sub>3</sub> ) OAc	F	ОН
00	CH (CH <sub>3</sub> ) OAc	CF <sub>3</sub>	ОН
	CO2CH (Me) OAc	Br	OH
	CO <sub>2</sub> CH (Me) OAc	Br ·	OAC
45	<del>-</del>		

## 15. Verbindungen nach Anspruch 11 der Formel

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worin die Substituenten wie in der nachstehenden Tabelle angegeben sind:

	R <sup>2</sup> _	<u>R</u> 3	R <sup>5</sup>
5			
_	Br	OMe	OMe
	Cl	OMe	OMe
	F	OMe	OMe
10	I	OMe	OMe
	CF <sub>3</sub>	OMe	OMe
15	CN	OMe	OMe
	Br	OEt	OEt
	Cl	OEt	OEt
	Br	OMe	OEŁ
	Cl	OMe	OEt
20	F	OMe .	OEt
	Br	OEŁ	OMe
	Cl	OEŁ	OMe
25	F ,	OEt .	OMe
	CF <sub>3</sub>	OEt	OMe

- 30
  16. 3-Acetoxy-10-acetyl-4-brom-2,7-dimethoxy-10H-phenothiazin.
  - 17. 10-(1-Acetoxyethoxycarbonyl)-4-brom-2,7-dimethoxy-3-hydroxy-10H-phenothiazin.
- 35 18. 3-Acetoxy-10-acetyl-4-chlor-2,7-dimethoxy-10H-phenothiazin.

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- 19. 4-Brom-2,7-dimethoxy-3-hydroxy-10-(1-pivaloyloxyethoxycarbonyl)-10H-phenothiazin.
- 20. 3-Hydroxy-10-(1-acetoxyethoxycarbonyl)-4-chlor-2,7-dimethoxy-10H-phenothiazin.
- 21. 3-Acetoxy-10-(1-acetoxyethoxycarbonyl)-4-brom-2,7-dimethoxy-10H-phenothiazin.
- 22. 3-Hydroxy-10-acetyl-4-brom-2,7-dimethoxy-10H-phenothiazin.
- 23. Zusammensetzung nach einem der Ansprüche 1 bis 9, welche zusätzlich eine wirksame Menge eines zweiten wirksamen Bestandteils umfaßt, der ein nicht steroides entzündungshemmendes Mittel; ein peripheres Analgetikum; ein Cyclooxygenaseinhibitor; ein Leukotrienantagonist; ein Leukotrieninhibitor; ein H<sub>2</sub>-Rezeptor-Antagonist; ein Antihistaminikum; ein Prostaglandinantagonist oder ein Thromboxanantagonist ist.
  - 24. Zusammensetzung nach Anspruch 23, worin das Gewichtsverhältnis der Verbindung der Formel I zum zweiten wirksamen Bestandteil im Bereich von 1000:1 bis 1:1000 liegt.
  - 25. Zusammensetzung nach Anspruch 24, worin das Verhältnis 200:1 bis 1:200 ist.

26. Zusammensetzung nach einem der Ansprüche 23 bis 25, worin der zweite wirksame Bestandteil ein nicht steroides entzündungshemmendes Mittel ist.

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	27.	Zusammensetzung thazin ist.	nach	Anspruch	26,	worin	das	nicht	steroide	entzündungshemmende	Mittel	Indome-
5												
10												
15												
20												
<b>2</b> 5												
30									-			
35												
40			-									
45												
50												
55												